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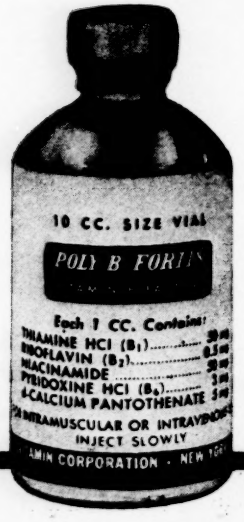

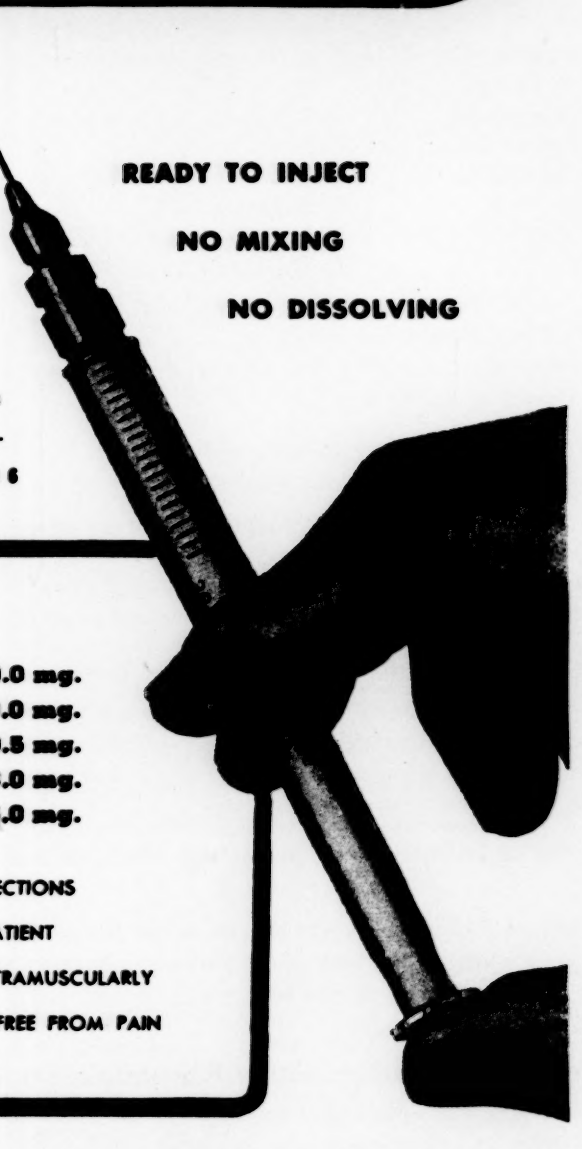

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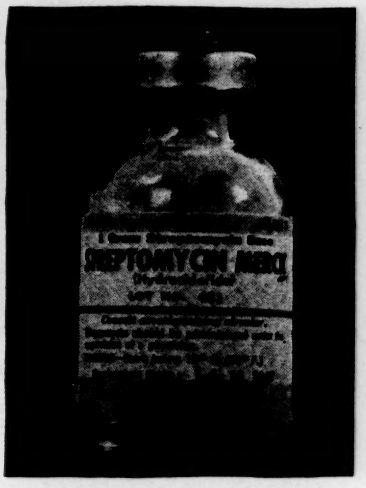

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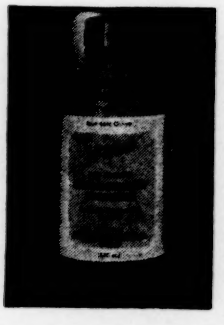

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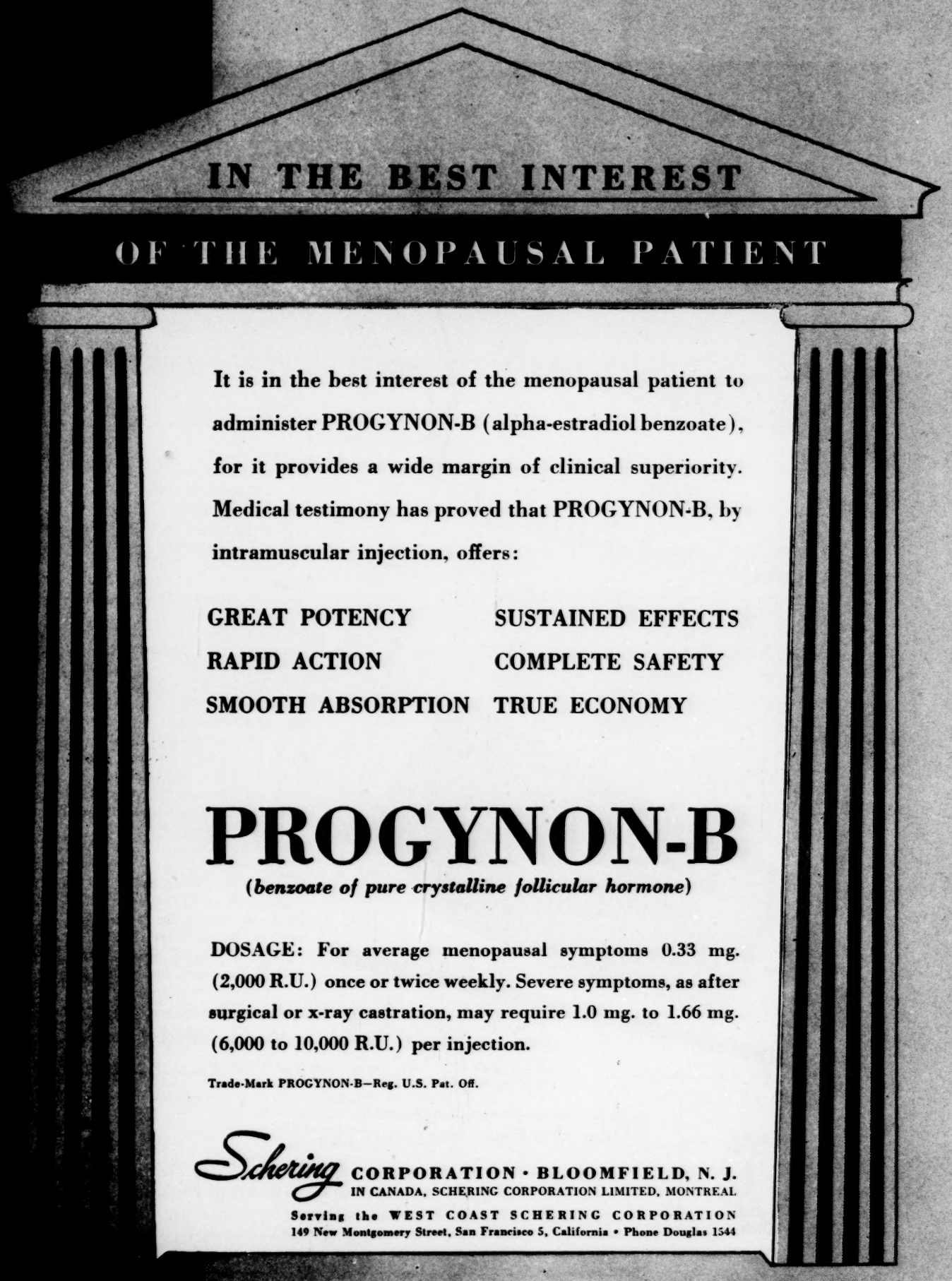

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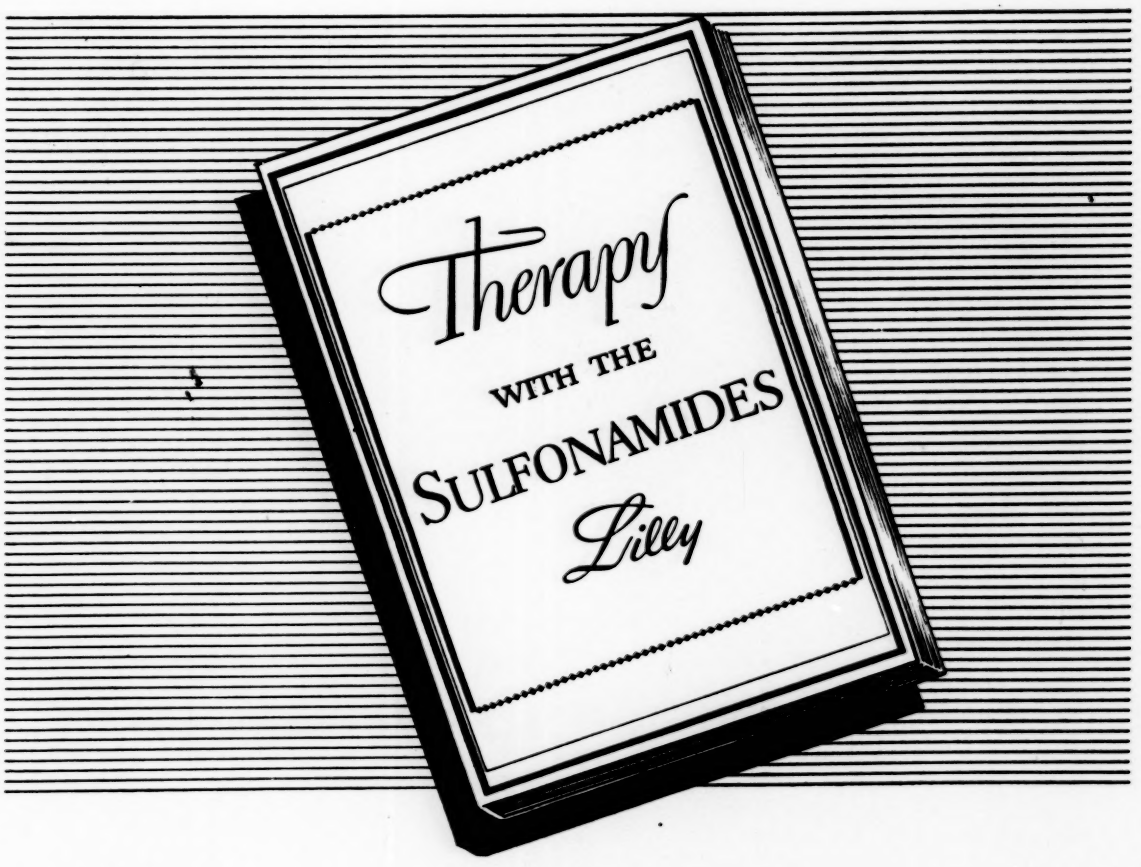

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The Influence of the Respiration on the Circulation in Man*

With Special Reference to Pressures in the Right Auricle, Right Ventricle, Femoral Artery and Peripheral Veins†

HENRY D. LAUSON, M.D., RICHARD A. BLOOMFIELD, M.D. *and* ANDRE COURNAND, M.D.
NEW YORK, NEW YORK

THE influence of the respiration on the pressures in the circulatory system has been the subject of numerous investigations during the past century. Relatively few, however, have been made on man, and most of these have been confined to observations on the systemic arterial and peripheral venous pressures. The development of a technic of catheterization of the right auricle and ventricle in man[1,2,3] made it possible to study pressure variations in these chambers. By means of simultaneous optical recording of right heart, femoral arterial and peripheral venous pressures, together with recording of respiratory movements, and in a few cases, of intrapleural pressure, a large amount of material has been accumulated, the description and analysis of which follow.

METHODS

Pressures were optically recorded by means of Hamilton[4] type manometers, as previously described.[3] Calibration curves for the venous and cardiac records were corrected so that the horizontal plane 5 cm. below the angle of Louis was taken as zero (atmospheric) pressure.[3] In most instances, the femoral plane of reference was the artery itself, which rarely differed from the above by more than 2 or 3 mm. Hg. All pressures are expressed in mm. Hg.

Unless otherwise indicated, the measurements were made with the patient recumbent with one pillow under the head. In the few cases in which the head and trunk were elevated, the zero reference plane for cardiac pressures was taken 5 cm. vertically below the angle of Louis. In a given patient, a single reference level was used for determining pressures in the antecubital vein, intrathoracic veins, right auricle and right ventricle.

Respiration was recorded by means of a modified Marey pneumograph connected by rubber tubing to a thin rubber mem-

* From the Department of Physiology of New York University College of Medicine and the Department of Medicine of the College of Physicians and Surgeons, Columbia University, and the Chest Service (Columbia University Division) of Bellevue Hospital, New York City.

† This work was carried on under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development, and Columbia University, with the collaboration of New York University. Additional support was provided by the Commonwealth Fund.

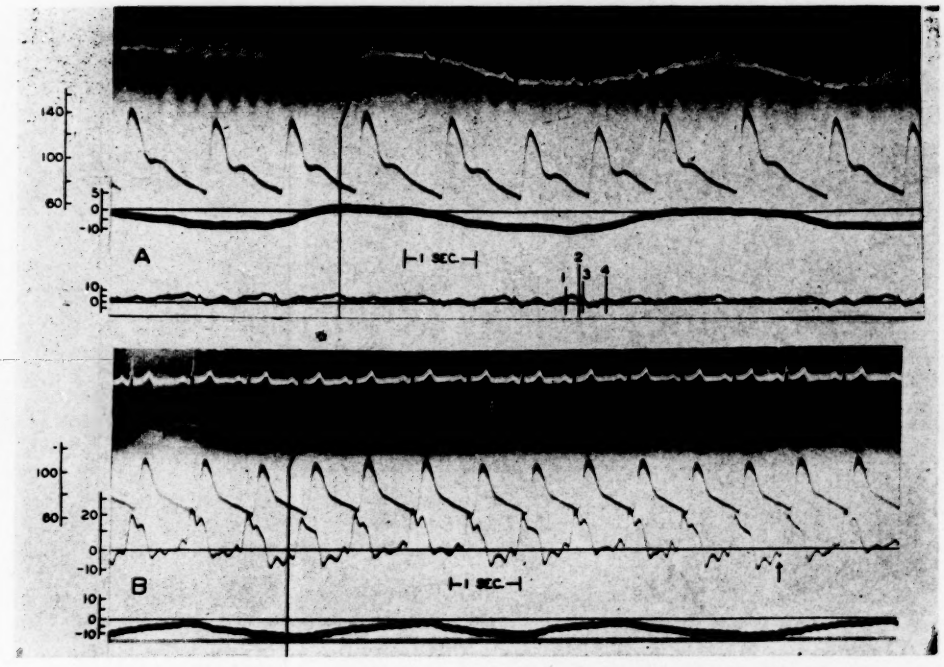

FIG. 1. *Influence of rhythmic respiration at slightly increased depth.* A, *from above downward, electrocardiogram, femoral arterial pressure, intrapleural pressure, and right auricular pressure from patient No.* 47. *In this and all subsequent figures, scales at left represent mm. Hg above and below atmospheric pressure, where the zero level of reference for intracardiac and venous pressures is taken to be* 5 *cm. below the angle of Louis. Patient numbers are the same as in* (3). *Parallax between electrocardiogram and pressure curves is indicated by vertical line in third cardiac cycle, drawn through beginning of ventricular complex of electrocardiogram. Events of auricular cycle are labelled as follows:* 1, *beginning of auricular systolic pressure rise;* 2, *positive wave associated with ventricular isometric contraction;* 3, *negative wave associated with onset of ventricular ejection; and* 4, *negative wave due to opening of tricuspid valve. There is a moderate degree of sinus arrhythmia which is discussed in connection with Figure* 15. B, *from above downward, electrocardiogram, femoral arterial pressure, right ventricular pressure and intrapleural pressure, from patient No.* 48. *Arrow at right indicates point at which ventricular pressure at end of diastole was measured in each cardiac cycle. This corresponds to the time in right auricular cycle labelled* 2 *in Figure* 1A. *Ventricular systolic pressure was measured at the highest point during each systole.*

brane in such a manner that changes in the chest circumference at the nipple level caused movement of a lever placed immediately in front of the camera. Lead II of the electrocardiogram was also recorded in most cases.

All pressures were recorded without parallax, but between the pressures on one hand, and the electrocardiogram on the other, parallax exists such that the latter appears about 0.13 seconds late. A line has been drawn in Figure 1 to indicate this parallax correction. Since no further reference will be made to the electrocardiogram in this report, a correction has not been made in the remaining figures.

In six patients the intrapleural pressure was recorded by means of a modified Hamilton manometer connected to an intrapleural catheter recently described.[5] In a few cases, pressures in the right auricle and ventricle were simultaneously recorded through a double-lumen catheter.[6]

CASE MATERIAL

The subjects were patients from all of the four divisions of Bellevue Hospital. Pressure tracings from over 200 patients

have been examined with regard to the influence of respiration, and representative records and data from eighteen of these are described in the present paper. The total series includes normal subjects and patients with chronic pulmonary disease (emphysema, fibrosis and tuberculosis), and patients with heart disease due to rheumatic fever, arteriosclerosis, hypertension and chronic pulmonary disease. The diagnosis is indicated in connection with each tracing discussed. The numbers designating the patients are the same as were used in the previous publication,[3] and reference is made to Table I of that paper for complete diagnosis and pressure data.

RESULTS AND INTERPRETATIONS

A. Influence of Rhythmic Respiration on the Pressures in the Intrathoracic and Peripheral Veins, the Right Auricle and Ventricle and the Femoral Artery. 1. Quiet breathing in normal subjects: As expected, only very slight rhythmic variations in pressure are observed during quiet breathing. Several records have been previously published. (Figs. 1A, 1B and 2 in ref.[3]) When the intrathoracic pressure varies only by a few mm. Hg, the vascular pressures vary but slightly, consistent with minimal changes in right heart filling and stroke volume and in the pulmonary vascular capacity.

2. Moderately deepened respiration: When the respiration is somewhat deeper, whether voluntary or involuntary, a more distinct pattern is seen. Figure 1 presents tracings from patients (Nos. 47 and 48) with recently induced pneumothorax in whom the pulmonary and systemic circulations are regarded as sufficiently normal to give an idea of the effects of this type of breathing in the normal subject.

In Figure 1A the intrapleural pressure during inspiration falls to a minimum of −7 mm. Hg, while in the right auricle the general level of pressure changes little. However, the amplitude of the auricular waves during the cardiac cycle increases during inspiration. The sudden fall of pressure associated with the beginning of ventricular ejection (beginning with the line numbered *3*) is much more prominent at the depth of inspiration than at the height of expiration. (Fig. 10.) In this illustration the difference between the pressure in the auricle at the end of diastole (line *2*) and that in the intrapleural space, i.e., the *net* pressure[7] is much greater (about 12 mm. Hg) during inspiration than during expiration (about 4 mm. Hg).

In Figure 1B, the pressures in the right ventricle at the end of diastole and at the peak of systole decrease with inspiration. The difference between these pressures on one hand, and the intrapleural pressure on the other, i.e., the net pressures, increases during inspiration, just as the net auricular pressure at the end of diastole increases in Figure 1A.

In Figures 1A and B, the systolic, diastolic and pulse pressures in the femoral artery are lowest when the intrapleural pressure is at a minimum, and greatest at the height of expiration. This is due in part to the direct effect of the intrapleural pressure on the intrathoracic aorta transmitted throughout the arterial tree. In these cases, if the concomitant intrapleural pressure is subtracted from the femoral systolic and diastolic pressures, the resultant net pressures still show a small decline with inspiration and a rise during expiration in the case of Figure 1A, and practically no change in Figure 1B.

If the stroke volume from the right ventricle varies as a function of the net auricular or ventricular pressure at the end of diastole (i.e., with the net pressure of the filled ventricle), records such as these would indicate an increase in right ventricular output during inspiration of moderately increased depth. The inspiratory increase in the net

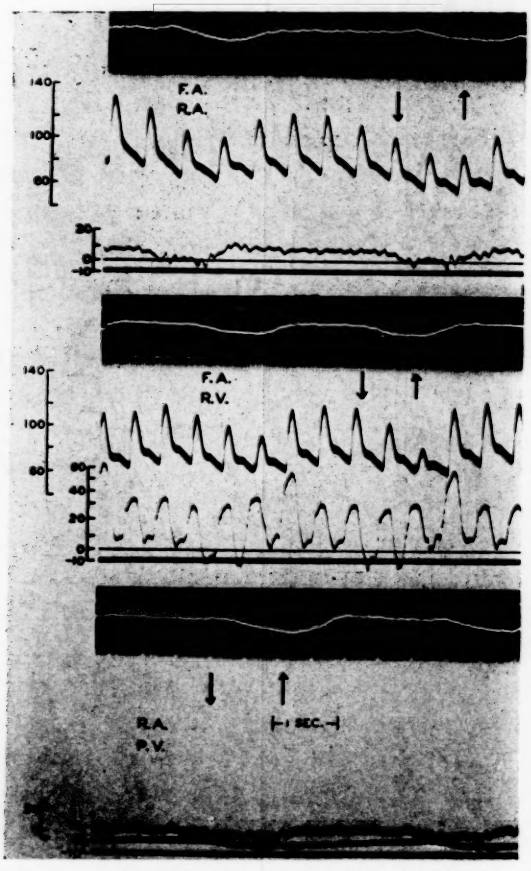

FIG. 2. *Natural breathing in chronic pulmonary disease. The three tracings are from patient No. 26. White curve above EGG is pneumogram; inverted black arrows indicate onset of inspiration and upright black arrows mark beginning of expiration. Upper record, femoral arterial and right auricular pressures; middle record, femoral arterial and right ventricular pressures; lower record, right auricular and peripheral venous pressures. Note ventricular premature contraction at beginning of both expirations of middle record, which results in a somewhat higher pressure in the succeeding beat than if rhythm had remained normal.*

systolic pressure in the right ventricle, as well as the greater pulse pressure (right ventricular systolic pressure minus the pressure at the end of the preceding diastole) are consistent with this view. Furthermore, if it may be assumed that the peripheral resistance is constant during the respiratory cycle, the small variations in the net arterial pressures may be attributed to variation in stroke volume from the left ventricle.

3. Natural breathing in chronic pulmonary disease: Because of the altered respiratory pattern associated with chronic pulmonary diseases, it is pertinent to examine some of the effects of respiration on vascular pressures in patients having such diseases. Figure 2 shows records from a patient with chronic pulmonary emphysema and fibrosis (No. 26) in whom the residual air, total lung capacity, and their ratio were 3620 ml., 5640 ml. and 64 per cent, respectively, as compared to the predicted normal values of 1195 ml., 4880 ml., and 24.5 per cent, respectively.[3] The three tracings were recorded while the patient was breathing naturally in the recumbent position. Without the simultaneous intrapleural pressure measurement in this case, it is not possible to describe with certainty how this labored type of breathing differs in its effects on the circulation from voluntarily deepened respiration in normal subjects. However, the upper and middle sections show a prominent waxing and waning of the pressure pulse in the femoral artery, the change in systolic, diastolic and pulse pressures being in the same direction as the presumed change in intrathoracic pressure. Although the right auricular pressure (upper section) varies in phase with the femoral, there is a greater amplitude of the auricular waves during inspiration, whereas the femoral pulse pressure is greater during expiration. The middle section shows that as the right ventricular diastolic pressure falls during inspiration, the amplitude of the succeeding ventricular pulse increases, suggesting an increased stroke volume during this phase. In the lower section, the simultaneous right auricular and antecubital venous pressures show that the gradient from arm to heart is greatest in inspiration and least, or even reversed, during expiration. These results are consistent with the classical concept that venous flow into the right heart is increased during inspiration and decreased during expiration.

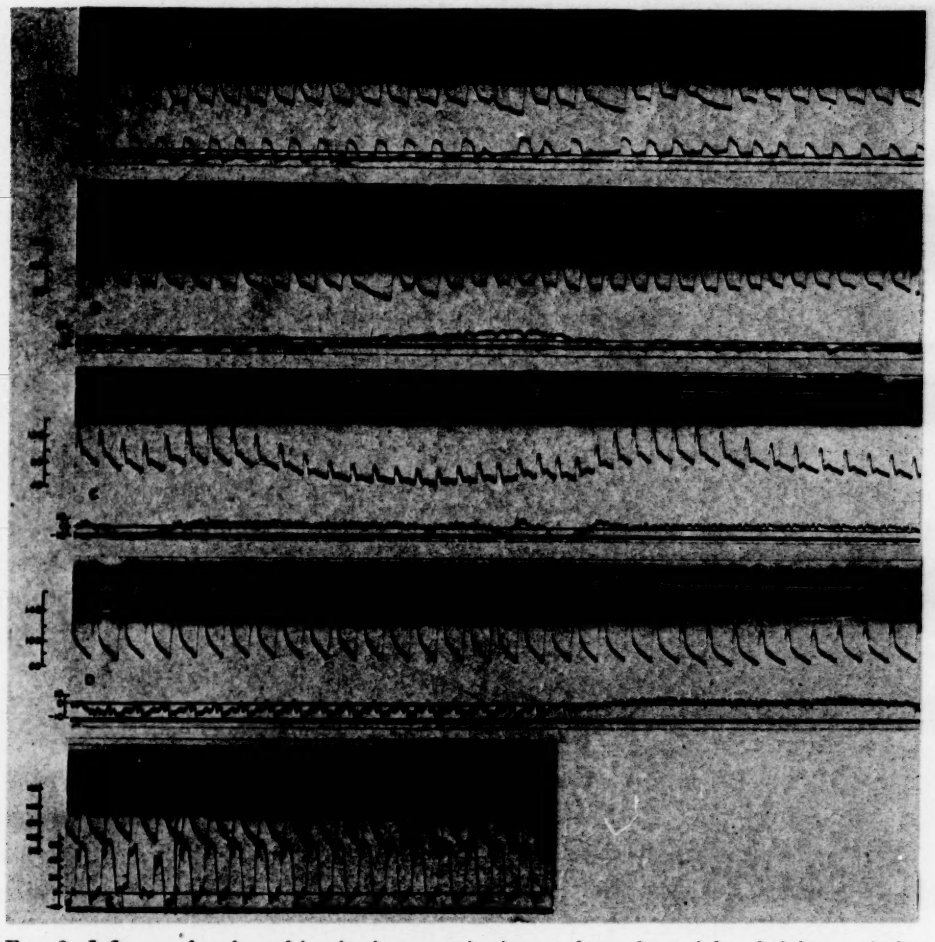

FIG. 3. *Influence of prolonged inspiration or expiration.* A, *femoral arterial and right ventricular pressures from patient No.* 43. *Left half, held inspiration; right half, held expiration. Note premature ventricular contractions during expiration, presumably due to mechanical stimulation by the catheter* (3). *The slow changes in the pneumogram are due to slow movement of air as the patient attempted to hold breath in inspiration or expiration while keeping glottis open.* B, *femoral arterial and right auricular pressures from same patient. Left, deep held inspiration; middle, expiration; right, inspiration.* C, *femoral arterial and right auricular pressures during short deep inspiration followed by prolonged expiratory effort in patient No.* 18. D, *femoral arterial and right auricular pressures in patient No.* 35 *during sustained inspiration (left) and sustained expiration (right). Note the striking change in auricular pattern.* E, *femoral arterial and right ventricular pressures from same patient as in* D, *during prolonged inspiration. White arrow at top marks onset of inspiration. The marked increase in right ventricular amplitude, corresponding to altered auricular pattern seen in* D, *is interpreted to mean augmented right ventricular discharge during deep inspiration.*

B. Sustained Inspiration and Expiration. In several cases, the patient was instructed to try to hold his breath with the glottis open, in a position either of deep inspiration or of forced expiration. Some examples are shown in Figures 3 and 4.

Figures 3A and B are from patient No. 43 who had a right fibrothorax, and in whom the circulation was considered to be essentially normal. Row *A* shows a prolonged deep inspiration in the left half, followed by a held expiration in the right half. The amplitude of the right ventricular pressure pulses is greater all through inspiration than during expiration. The general level of femoral pressure is slightly lower during

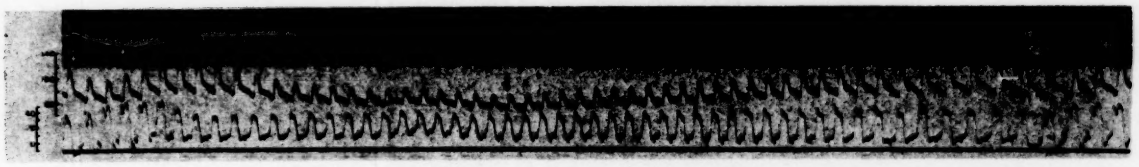

FIG. 4. *Effect of sustained expiration. Femoral arterial and right ventricular pressures in patient No. 26, during prolonged expiration which continues until the fourth beat from the right. The upright white arrow at left indicates onset of prolonged expiration, and inverted white arrows denote onset of inspiration. Inverted black arrow near middle marks beginning of pressure increase described in text.*

inspiration, but no change in pulse pressure is seen, except as associated with the premature ventricular contractions. In Row *B* which shows the effect of successively held inspiration, expiration and inspiration on the right auricular pressure, the larger amplitude of the pressure waves during inspiration is again noted.

Row *C* in Figure 3 illustrates a striking alteration in the arterial pressure of a patient with chronic pulmonary emphysema (No. 18). Early in expiration the femoral systolic, diastolic and pulse pressures increase as in Figures 1A and 2. However, after a few beats, the femoral pressures fall dramatically to a level at which the systolic pressure is less than the diastolic value of a few beats previously. Although the intervention of the carotid and aortic pressor reflexes cannot be excluded, it is noteworthy that there is no change in heart rate.

Another example from a patient with diffuse nodular pulmonary fibrosis (No. 35) is shown in rows *D* and *E* of Figure 3. Here the sustained inspiration produces the characteristic auricular and ventricular patterns suggesting increased right heart output. Within the first few inspiratory beats there is an increase in femoral systolic and pulse pressures which is maintained throughout inspiration. With the onset of expiration (row *D*) the amplitude of the auricular waves promptly decreases and the femoral systolic and pulse pressures fall and then remain stabilized at the lower level.

Figure 4 (patient No. 26, same as in Figure 2) is of special interest because the expiration was held for a long time (26 seconds). It will be noted that after the twenty-fifth beat 10 seconds after the onset of expiration (indicated by the black arrow), the amplitude of the right ventricular pressure pulse begins to increase again, and after several beats there is a progressive rise in arterial systolic, diastolic and pulse pressures. This suggests that as the flow into the thorax is impeded, the volume of the peripheral venous reservoir slowly increases until the venous pressure becomes sufficiently great again to increase the right heart filling and output, in spite of the continued elevation of the intrathoracic pressure. During the next inspiration a further augmentation of the right ventricular pulse pressure occurs in the last four beats.

The upper section of Figure 5 (same patient as in Figures 2 and 4) shows the changes in pressure gradient between the peripheral vein and the right auricle during prolonged expiration. At the depth of the preceding inspiration, the gradient is +5 mm. Hg, but it promptly reverses with the onset of expiration. Thus flow from the arm veins into the thorax is arrested, or at least retarded, until the venous pressure gradually rises to exceed that in the right auricle. This occurs near the end of the tracing, at a time corresponding approximately to the beginning of the femoral pressure increase seen in the middle of the expiratory period in Figure 4.

The second and third sections of Figure 5 reveal that when the catheter is withdrawn into the superior vena cava, and then into

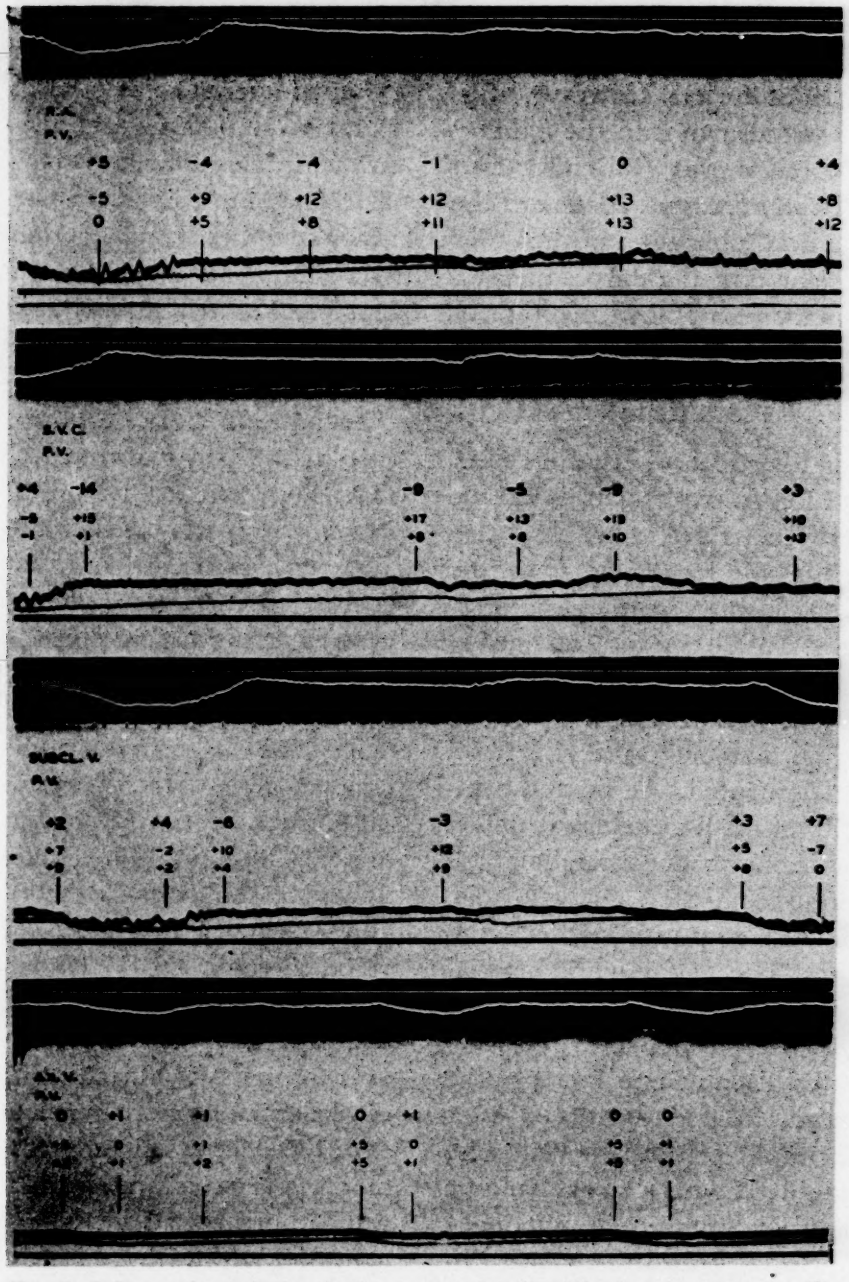

FIG. 5. *Influence of sustained expiration on central and peripheral venous pressures. All four tracings are from patient No.* 26. *Upper record, right auricular (heavy tracing) and peripheral venous pressures; second record from top, superior vena cava (heavy tracing) and peripheral venous pressures; third record, subclavian (heavy tracing) and peripheral venous pressures; lower record, axillary (heavy tracing) and peripheral venous pressures. The peripheral venous pressure was recorded through a needle inserted into the antecubital vein of the arm opposite to that in which catheter was placed. In each record, the upper numbers indicate the pressure gradient between the antecubital vein and the more central vein. The middle numbers refer to the actual pressure in the indicated central veins, while the lower numbers denote the antecubital pressures. The zero level of reference was the horizontal plane* 5 *cm. below the angle of Louis for each pair of tracings.*

the subclavian vein, the pattern during deep inspiration and sustained expiration is the same as in the right auricle. However, after the catheter is withdrawn into the axillary vein outside of the thorax (lower section) the picture abruptly changes. Although the depth of inspiration is less than in the other tracings, it is clear that the curves of pressure in the axillary vein and in the antecubital vein (of the opposite arm) remain practically identical throughout the respiratory cycle.

Summarizing the effects of sustained deep inspiration and forced expiration, it can be stated that the results are consistent with those seen in rhythmic breathing. Thus, the greater negativity of the intrathoracic pressure in inspiration increases the capacity of the intrathoracic great veins and right heart chambers. Right ventricular output increases, and the net pulmonary arterial pressures are augmented. At first, the increased capacity of the pulmonary vessels is more than sufficient to accommodate the increased volume from the right ventricle, and the filling and output of the left ventricle diminishes. The net systemic arterial pressures fall as a consequence. After a few beats, however, the pulmonary vessels become sufficiently distended to increase the filling and output of the left ventricle. After this time, the output of the two ventricles tends to be stabilized with a stroke volume greater than normal, and the net pulmonary and systemic arterial pressures remain elevated. The mean volume of blood contained in the pulmonary vessels during this period of equilibrium must be greater than normal.

Sustained expiration results in the converse changes. Impeded venous return secondary to compression of the intrathoracic great veins and the right heart chambers leads to decreased right ventricular output and decreased net pulmonary arterial pressures. The pulmonary vessels are compressed at first and displace an extra amount of blood into the left ventricle, increasing its output temporarily and raising the net systemic arterial pressures. Soon equilibrium is established and the output of the two ventricles tends to become equalized at a stroke volume less than normal. After this time the net systemic arterial pressure drops to a subnormal level. The mean volume of blood contained in the pulmonary vessels during this period of equilibrium must be less than normal.

Inspiration causes a prompt fall of pressure in the peripheral as well as the intrathoracic veins, as a direct result of the increased capacity of the intrathoracic veins and right heart. During expiration, however, a direct retrograde effect of the increased intrathoracic pressure is blocked by venous valves. Therefore, the rise in peripheral venous pressure is very gradual, being only a secondary effect of the increased intrathoracic pressure. The latter diminishes the central venous capacity and impedes venous return; as a result blood slowly accumulates in the peripheral veins and gradually raises the pressure of the blood therein.

All of the changes described above are essentially dependent on the displacement of increments of blood into and out of the intrathoracic vessels, particularly from the extrathoracic systemic veins into the pulmonary arteries and from the pulmonary veins into the systemic arteries through the operation of Starling's law. The force causing the displacements resides in the muscles of respiration. The simple basic pattern described, although subject to modification by cardiovascular reflexes and possibly other factors, is nevertheless discernible in practically every record.

C. Exaggerated Forms of Respiration. 1. The Valsalva experiment: Figure 6 illustrates some results of this maneuver on the pressures in the right heart and femoral artery.

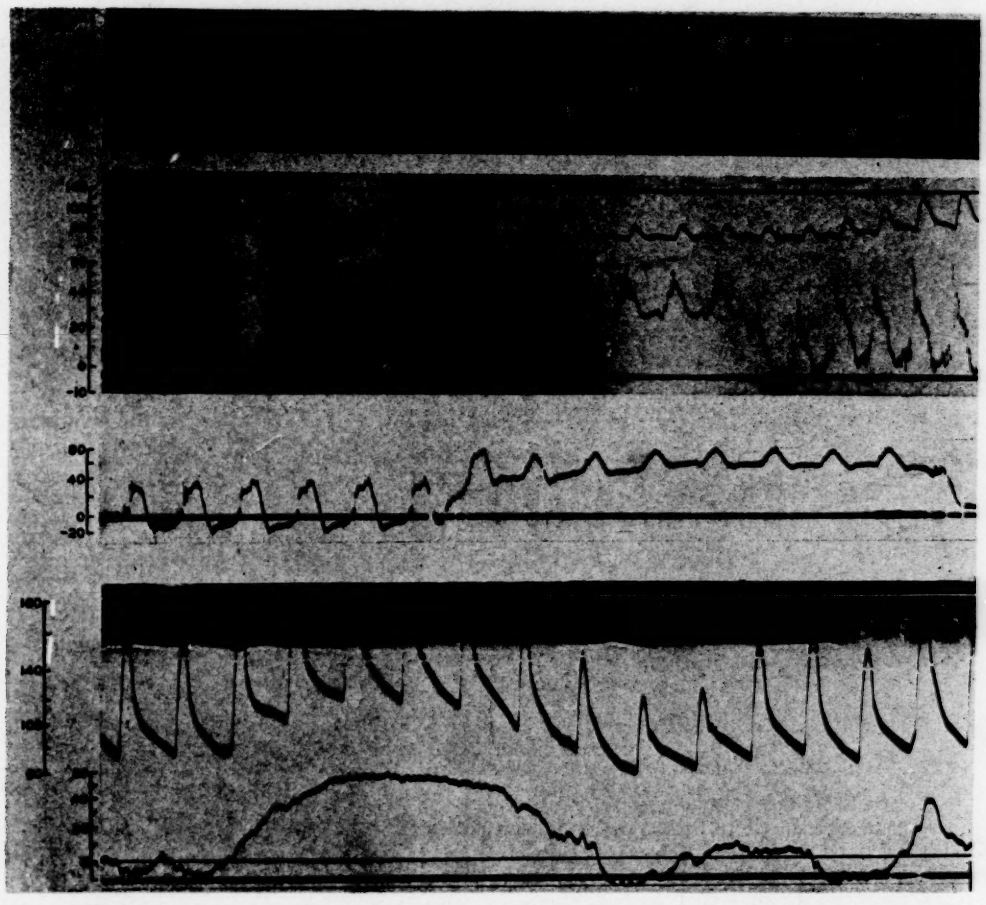

FIG. 6. *Valsalva experiment. The upper record is an approximation of the net right ventricular pressure obtained by having the normal subject blow forcibly into tubing connec d to front chamber of differential manometer. The strain begins with the fifth beat. The manometer employed in this case was less sensitive than those used in most of the studies. Second record shows "net" femoral arterial (femoral minus mouth pressures) and "total" right ventricular pressures during similar effort in same subject. The higher frequency oscillations are artefacts. Third section shows effect of Valsalva maneuver on total right ventricular pressure in patient No.* 19, *who had severe chronic pulmonary emphysema. Lowermost section shows femoral arterial and right auricular pressures from patient No.* 23 *during strain.*

In order to estimate the changes in net pressures in the right ventricle and femoral artery, mouth pressure, substituted for intrapleural pressure, was transmitted through a connecting tube to the front chamber of a differential manometer.[8,9] The upper row of Figure 6, recorded by this method, shows clearly that the "net" pressure in the right ventricle of a normal subject decreases markedly during the strain. In the second row, the total right ventricular pressure (lower tracing) during a similar effort in the same patient is recorded together with the "net" femoral arterial pressure pulses (upper tracing). The elevation of the ventricular diastolic pressure indicates the approximate level of the intrathoracic pressure. The rather abrupt decrease in the amplitude and "fullness" of the ventricular pulse is similar to that in the upper row. The "net" femoral (femoral arterial minus mouth pressure) pressure falls after a brief lag, and the pulse pressure becomes markedly reduced. The same lag is seen after cessation of the strain between the recovery of the right ventricular and the femoral pulse amplitudes, as shown in Figure 6 above.

FIG. 7. *Mueller experiment. Upper curve (heavy black) is intrapleural pressure recorded from a pneumothorax induced twenty-three days previously and last refilled a week prior to study; middle curve, right auricular pressure (retouched to improve contrast); lower curve, right ventricular pressure. The scales at left are:* P, *intrapleural;* A, *right auricular; and* V, *right ventricular. The intrapleural pressure, net ventricular pressure at end of diastole, and net ventricular systolic pressures, respectively, for the four cycles marked by vertical lines are as follows:* 1, − 0.5, + 3.0, *and* + 22.5 *mm. Hg;* 2, − 21.5, + 5.5, *and* + 36.5 *mm. Hg;* 3, − 7.0, + 4.5, *and* + 31.0 *mm. Hg; and* 4, − 3.5, + 3.5, *and* + 28.0 *mm. Hg.*

The third row shows the effect of a Valsalva maneuver on the right ventricular pressure of a patient with severe pulmonary emphysema (No. 19). The result is similar to that in the normal subject.

The first three rows of Figure 6 are consistent with the concept that a strong compression of the thoracic contents impedes venous return and, as a consequence, diminishes the right ventricular stroke volume. After a brief delay the output of the left ventricle also decreases. This interpretation accords with the conclusions of investigations recently reviewed by Liedholm[10] and of Hamilton, Woodbury and Harper.[7,9]

The fourth tracing shows the effect of a brief Valsalva effort on the right auricular and femoral arterial pressures in another patient with chronic pulmonary emphysema (No. 23). The magnitude of the rise in both pressures is almost identical, clearly demonstrating that the immediate changes are largely the direct result of the increased intrathoracic pressure on the right auricle and aorta. Because of the short duration of the effort, sufficient blood continues to be displaced from the pulmonary bed to sustain the left ventricular output. Therefore, the amplitude and "fullness" of the femoral pulse does not diminish greatly during the strain. The reduced pulse pressure in the beat during the post-Valsalva inspiration is the effect of a normal deep inspiration, exaggerated by a decrease in venous supply to the left ventricle.

2. The Mueller experiment: Inspiratory effort against a closed glottis produces a marked fall in intrathoracic pressure. An example is shown in Figure 7 from patient No. 46 in whom the right auricular and ventricular pressures were recorded through a double-lumen catheter simultaneously with the intrapleural pressure. The inspiratory effort begins during the sixth beat and immediately all three pressures fall sharply. During the rest of the tracing the pressures gradually rise as the patient fails to sustain the extreme inspiratory effort noted at the beginning. Careful measurements reveal that the *net* right ventricular pressures as measured at the end of diastole and at the peak of systole are increased during this period of exaggerated inspiratory effort. This is taken to indicate increased output of the right ventricle.

3. Cough: Two examples of the effects of cough are presented in Figure 8 (patients No. 46 and 48). The changes are mainly due to the direct compression of all intrathoracic (and intra-abdominal) vascular

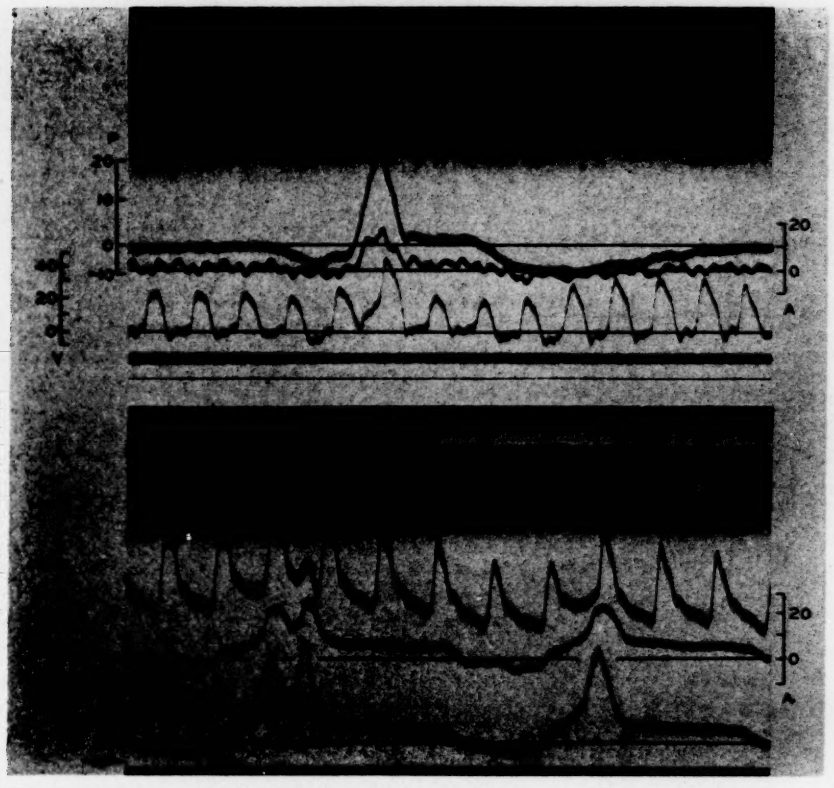

FIG. 8. *Effect of cough on right heart and arterial pressures. Upper record shows from above downward the ECG, intrapleural pressure, right auricular pressure, and right ventricular pressure, from patient No. 46. Lower record shows ECG, femoral arterial pressure, right auricular pressure, and intrapleural pressure, from patient No. 48. Scales are labelled as in Figure 7. It is apparent that the alterations of all the blood pressure curves are due chiefly to the algebraic addition of the curves of intrapleural pressure.*

structures by the abrupt rise in intrathoracic (and intra-abdominal) pressure. The blood pressure curves are to a large extent simply the normal curves modified by the algebraic addition of the intrathoracic pressure curve. Reference is made to the papers of Hamilton, Woodbury and Harper[7,9] for a more extensive analysis of the effects of cough.

The influence of coughing on the venous system was investigated in a few patients. The upper three and the lower left tracings in Figure 9 were obtained from the same patient as in Figures 2, 4 and 5. The pressures in the right auricle, superior vena cava, subclavian and axillary veins, respectively, are compared to that in the antecubital vein during coughs of varying intensity and duration. The intrathoracic veins show immediate rises in pressure, while the peripheral venous pressure remains practically unaffected. After the catheter is withdrawn into the axillary vein, the pressure is as little influenced as in the more peripheral vein (recorded in the opposite arm). In the presence of competent venous valves, the retrograde pressure wave set up in the thorax by the cough disappears somewhere near the entrance into the thorax of the axillary vein. Because the blood volume was normal and the venous system not overdistended, no important rise in peripheral venous pressure due to damming back is seen during the cough. This observation finds ready explanation in the fact that the partially filled vein can undergo a remarkable volume increase with practically no increase in pressure.[11]

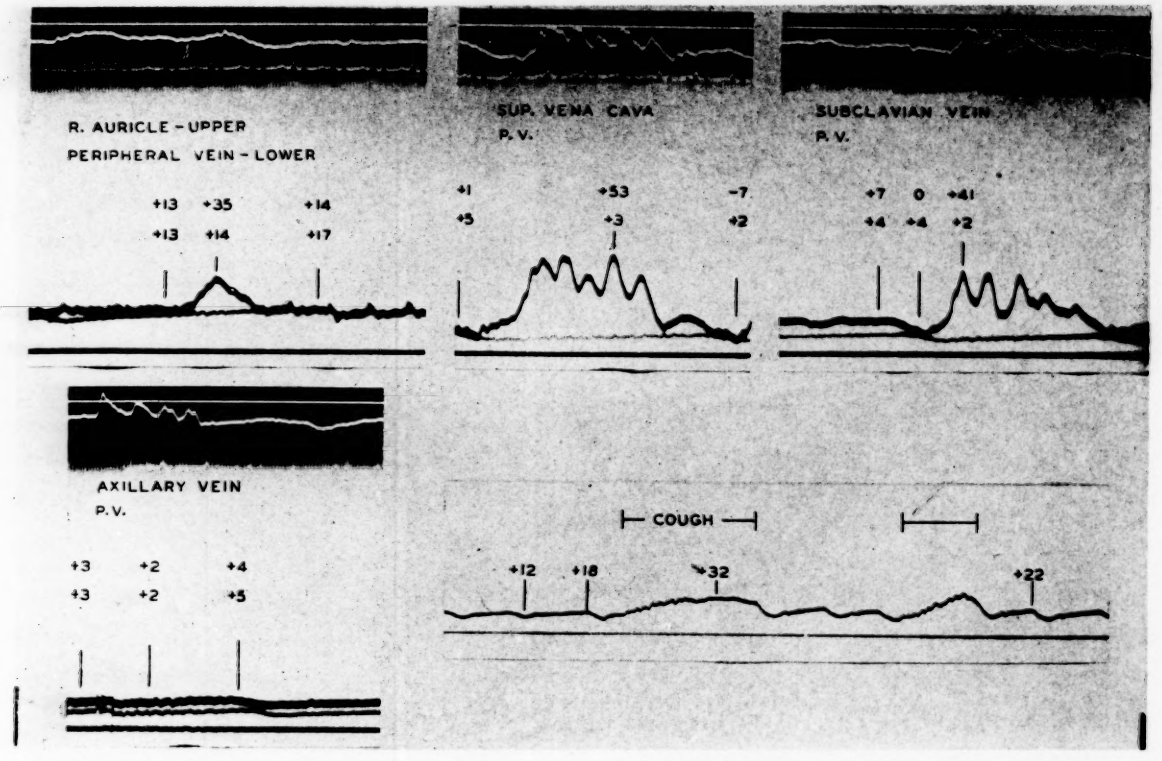

FIG. 9. *Influence of cough on the venous system. The upper three and lower left records are from patient No.* 26 (*same as in Figures* 2, 4 *and* 5). *In each section, the lower numbers indicate the peripheral venous pressure at the times noted, while the upper numbers refer to pressures in the right auricle, superior vena cava, subclavian and axillary vein, respectively. The high initial pressure in the upper left section is due to the fact that cough came at end of prolonged expiration. Note that there is little or no effect on axillary venous pressure, in spite of the fact that pneumogram indicates episode of coughing similar to that in upper middle and right sections. Lower right tracing is from antecubital vein of patient No.* 54, *who was in congestive heart failure. Contrast with lower left section.*

In the presence of an overfilled venous system associated with congestive heart failure (patient No. 54), a similar episode of coughing results in a relatively prompt elevation of the peripheral venous pressure, as shown in the lower right tracing of Figure 9. Since the veins were much nearer their limit of distensibility than in the more normal subject, the most probable explanation is that relatively little blood dammed back quickly raises the venous pressure.

D. The Influence of Deep Respiration on the Form of the Right Auricular Pressure Pulse in Various Clinical Conditions. Several types of response of the right auricular pressure to deep respiration are illustrated in Figure 10.

In *A*, a normal woman (patient No. 4) breathed very deeply while in the recumbent position. The remarkable excursion of almost 30 mm. Hg in the auricular pressure implies an even greater change in the intrathoracic pressure. The record shows numerous oscillations, some of which may be artefacts, and since no electrocardiogram was recorded simultaneously, only two waves can be identified with certainty. However, the waves show a larger amplitude during inspiration, which is believed to indicate an increased net pressure and greater right heart filling and output.

Tracing *B* was taken in a normal young woman (patient No. 15) sitting up in bed with the legs extended. In contrast to tracing *A*, the general level of pressure is not greatly influenced by deep inspiration. However, the depth of the wave corresponding to the onset of ventricular ejection, *3*, is increased during this phase. This pat-

tern is probably related to an increased net filling pressure and stroke volume in the right heart due to a large abdominal-thoracic pressure gradient associated with the posture and the abdominal type of breathing.

The next record, *C*, is from a patient with severe chronic pulmonary fibrosis (No. 33), breathing deeply while in the recumbent position. There is a general resemblance to *A*, but the waves are more prominent, and are strikingly increased in amplitude during inspiration.

Tracing *D*, from patient No. 38 with congestive heart failure secondary to chronic pulmonary disease, taken with the patient in an almost horizontal position, shows markedly deeper negative waves in inspiration than in expiration. This seems to indicate that even in cases in which the distended venous reservoir provides a high constant head of pressure at the right heart, the changes of intrathoracic pressure play an important part in modifying the filling and output of the right heart.

The last tracing, *E*, is perhaps the most interesting of the group. It was recorded in a patient (No. 51) with congestive heart failure, auricular fibrillation and tricuspid incompetency, secondary to rheumatic heart disease. During quiet respiration, the tracing, not shown here, was characteristic of tricuspid insufficiency.[3] During deep inspiration with the patient semi-recumbent, the striking feature is that the pressure in the auricle, instead of falling or remaining at the same level, rose to the unusual height of 60 mm. Hg (*ca.* 800 mm. water). In addition, the negative waves were very deep during inspiration. The two following factors are probably involved in this particular pattern: (1) the distended venous system, including the right auricle, is operating in that region of the volume-pressure curve in which a small increment of volume produces a large increment of pressure;[11] and

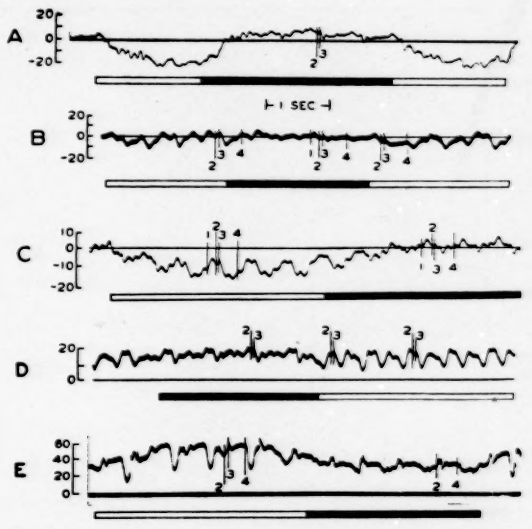

FIG. 10. *Influence of forced respiration on the right auricular pressure pulse. Solid horizontal column corresponds to expiration, and the open column to inspiration. Waves of auricular cycle are labelled as in Figure* 1A. A, *normal female* (*No.* 4), *recumbent;* B, *normal female* (*No.* 15), *sitting up in bed;* C, *patient with chronic pulmonary fibrosis* (*No.* 33), *recumbent;* D, *patient with congestive heart failure* (*No.* 38), *recumbent;* E, *patient with severe congestive heart failure, auricular fibrillation and tricuspid insufficiency* (*No.* 51) *in bed with head and trunk elevated about* 20°.

(2) the increase in intra-abdominal pressure exceeds the decrease in intrathoracic pressure, with the resulting displacement of a larger amount of blood into the right auricle than can be accommodated isotonically. An additional factor might be an increase in the magnitude of the tricuspid regurgitation during inspiration, related to a greater right ventricular stroke volume. The latter is suggested by the increased amplitude of the ventricular pulse pressure in tracings not shown here.

E. Detailed Analysis of Simultaneous Pressures in the Pleural Space, Right Heart and Femoral Artery. A continuous record of the intrapleural pressure was obtained in four patients with recently induced pneumothorax. This curve, recorded simultaneously with the right heart and femoral arterial pressure pulses, makes possible the measurement of the net pressures for successive heart beats during the respiratory cycle.

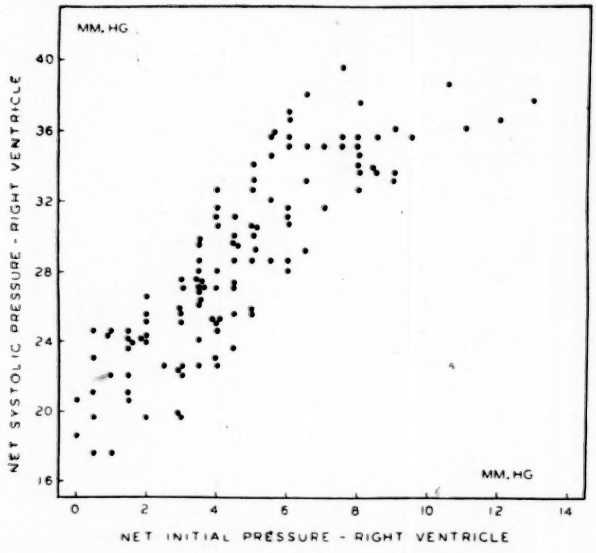

FIG. 11. *Relationship between net initial and net systolic pressures in the right ventricle. Abscissa, net pressure in right ventricle measured at the end of diastole (i. e., net initial pressure); ordinate, net pressure at the peak of the subsequent systole. Data are from* 123 *cardiac cycles recorded from patient No.* 46 *during several types of respiration. Records from which some of these data were obtained are shown in Figures* 7 *and* 8. *All cycles were measured except a few in which there were artefacts or in which the change of pressure was too rapid to permit accurate identification of the exact end of diastole or peak of systole. It is clearly seen that the greater the net initial pressure in the filled ventricle, the greater is the response during the subsequent contraction.*

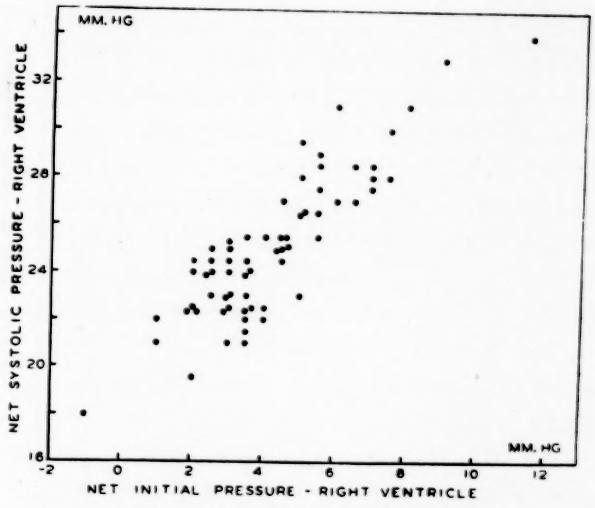

FIG. 12. *Relationship between net initial and net systolic pressures in the right ventricle. Measurements from sixty-five cardiac cycles in patient No.* 45 *are plotted as in Figure* 11. *The intrapleural pressure varied from* −14 *to* +6 *mm. Hg during several types of breathing.*

The pressure in the right auricle or ventricle was measured to the nearest ½ mm. Hg at the end of diastole. The intrapleural pressure at the same instant was subtracted to give a value representing the net pressure in the filled right heart. This net pressure at the end of diastole will be referred to as the "initial" pressure. Similarly, the maximum pressure developed in the right ventricle during the subsequent systole was measured, and by subtracting the concurrent intrapleural pressure, the value of the net systolic pressure was determined.

The net initial and net systolic pressures were measured in four groups of successive cardiac cycles in patient No. 46, during which intervals the patient breathed first at normal rate and slightly increased depth, then at normal rate and greatly increased depth, coughed and then performed a Mueller experiment. The intrapleural pressure varied from −21.5 to +8.5 mm. Hg. The results are plotted in Figure 11. The relationship is clear and demonstrates the essential feature of Starling's law in the right ventricle of man under physiological conditions. The greater the initial pressure (a function of the muscle fiber length), the greater the pressure developed (a function of the energy liberated by the contracting ventricle), and therefore, quite probably, the greater the volume of blood ejected into the pulmonary artery. The same measurements made in a second patient (No. 45) produced the similar result shown in Figure 12.

Another way of demonstrating the relationship between net right ventricular pressures and the intrapleural pressure in patient No. 46 is shown in Figure 13. The values for intrapleural pressure, measured at the end of diastole in three groups of successive heart beats, are plotted equidistantly in the

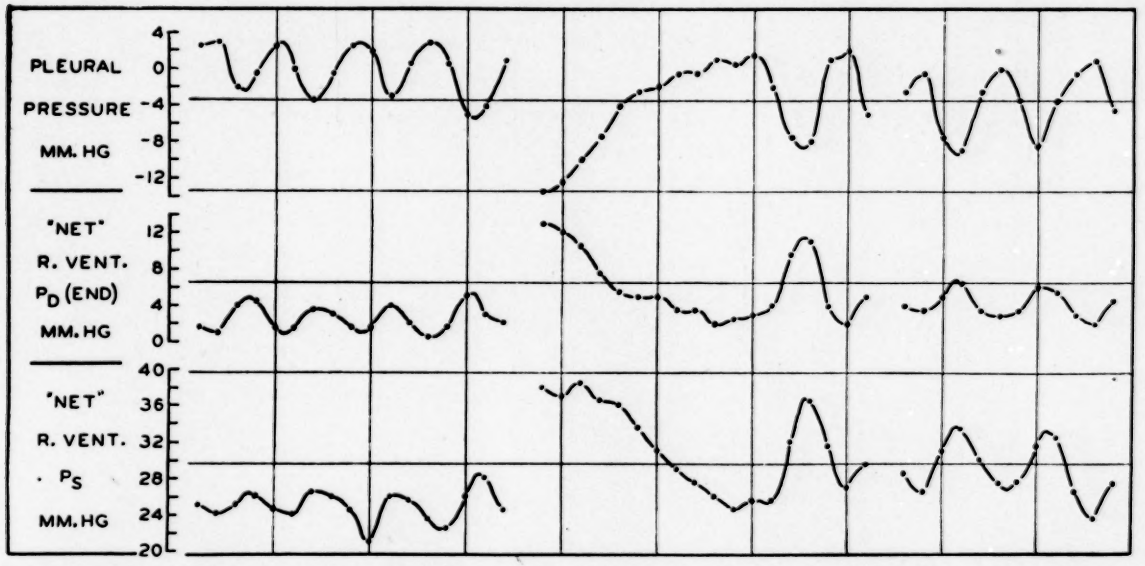

FIG. 13. *Relationship of net right ventricular pressures to intrapleural pressure. Upper row, values of intrapleural pressure as measured at end of ventricular diastole connected by smooth curve; middle row, net initial pressure in right ventricle; lower row, net systolic pressure in right ventricle. Left group, rhythmic breathing at normal rate and slightly increased depth, expiration being active. Center group begins with second heart beat after onset of a Mueller experiment similar to that shown in Figure 7, and proceeds through period of gradual relaxation of thoracic wall (slowly rising intrapleural pressure), a passive expiration, a deep inspiration and finally, a slightly forced expiration. Right group represents two deep rhythmic inspirations.*

upper row and are connected by a smooth curve. The net pressures in the right ventricle at the end of diastole of the same cardiac cycles are plotted in the middle row, and the net systolic pressures attained during the subsequent systoles are plotted in the lower row. The two ventricular curves are parallel, illustrating in another way the relationship already seen in Figure 11. Both of these curves, moreover, are almost exactly the inverse of the curve of intrapleural pressure, not only from beat to beat, but also over longer periods. Thus, when the entire respiratory cycle of the left-hand group is carried out in the pleural pressure range of −3 to +3 mm. Hg, the net right ventricular pressures are lower than in the right-hand group where the pleural pressure range was −9 to 0 mm. Hg.

With simultaneous recording of pressure in the right auricle and ventricle, using the double-lumen catheter, it is possible to demonstrate that at the end of diastole the pressures are identical in both chambers,

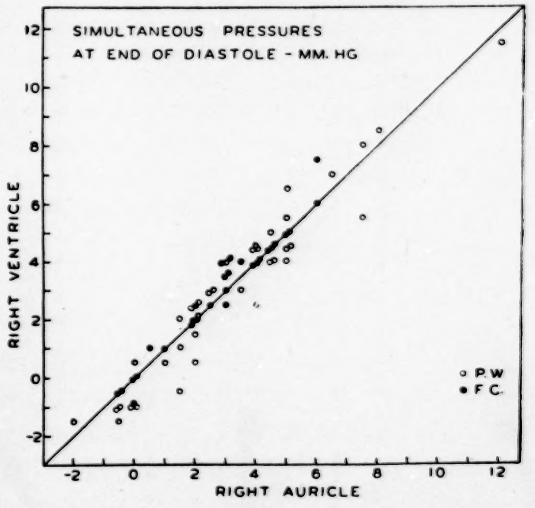

FIG. 14. *Comparison of simultaneous pressures in right auricle and right ventricle, both measured at end of diastole. Data represent sixty-eight cardiac cycles from patients No.* 45 (*P. W.*) *and No.* 46 (*F. C.*). *The agreement is sufficiently good to permit use of right auricular pressure as an indication of variation of right ventricular pressures.*

within limits of error of the method. This is shown in Figure 14. Variations in net right auricular pressure at the end of diastole may therefore be used as an indication of

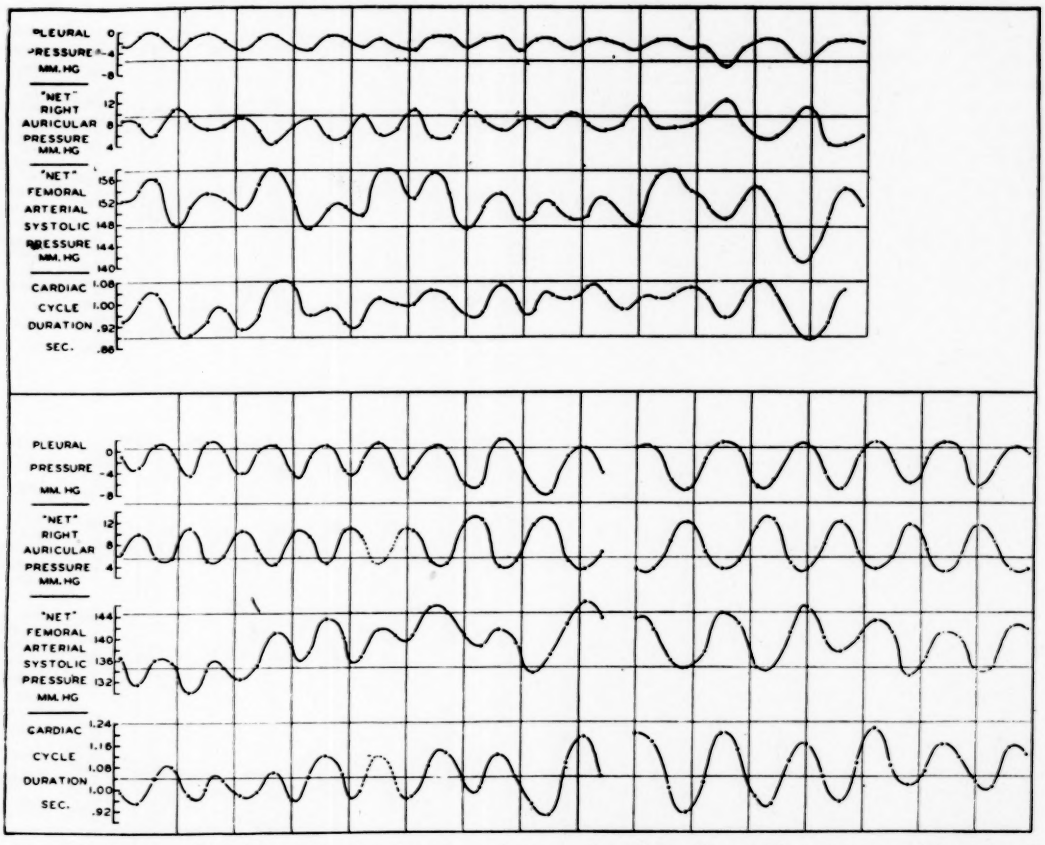

FIG. 15. *Relationship of intrapleural, net right auricular and net femoral arterial pressures, and duration of cardiac cycle. Data are from patient No.* 47 *with pulmonary tuberculosis, grade* IIB, *and a right pneumothorax induced ten days previously. Graphs of upper half are from records taken during quiet breathing prior to refill of pneumothorax. Top curve, intrapleural pressure values at end of ventricular diastole plotted equidistantly; second curve, net pressure in right auricle at end of ventricular diastole; third curve, net systolic pressure in femoral artery of subsequent contraction; fourth curve, duration of same cardiac cycle in which femoral systolic pressure was measured. The lower half of the figure shows results from tracings recorded immediately after a* 500 *ml. refill of air. On left, breathing at normal rate but moderately increased depth is shown, while on right respirations are still deeper.*

the variation in right ventricular stroke volume. This was done in the analysis of tracings from patient No. 47, shown in Figure 15. An almost perfect inverse relationship is demonstrated between the intrapleural pressure and the net right auricular pressure at the end of diastole, similar to that seen in Figure 13 between the intrapleural pressure and the net right ventricular pressures. The variations in the net femoral systolic pressures are seen to be in phase with the intrapleural pressure curve, but in addition, show slow undulations at periods considerably longer than a single respiratory cycle. These are assumed to represent changes in the activity of the vasomotor centers.[12] No such undulations modify the curves of right auricular pressure.

If it is assumed that the peripheral resistance in both lesser and greater circulations is essentially constant during any given respiratory cycle, it may be concluded (1) that during rhythmic breathing in this patient the left ventricular output is greatest when the intrapleural pressure is highest, and least when the intrapleural pressure is lowest, and conversely, (2) that the right ventricular output is greatest during inspiration and least during expiration.

Because of the marked sinus arrhythmia

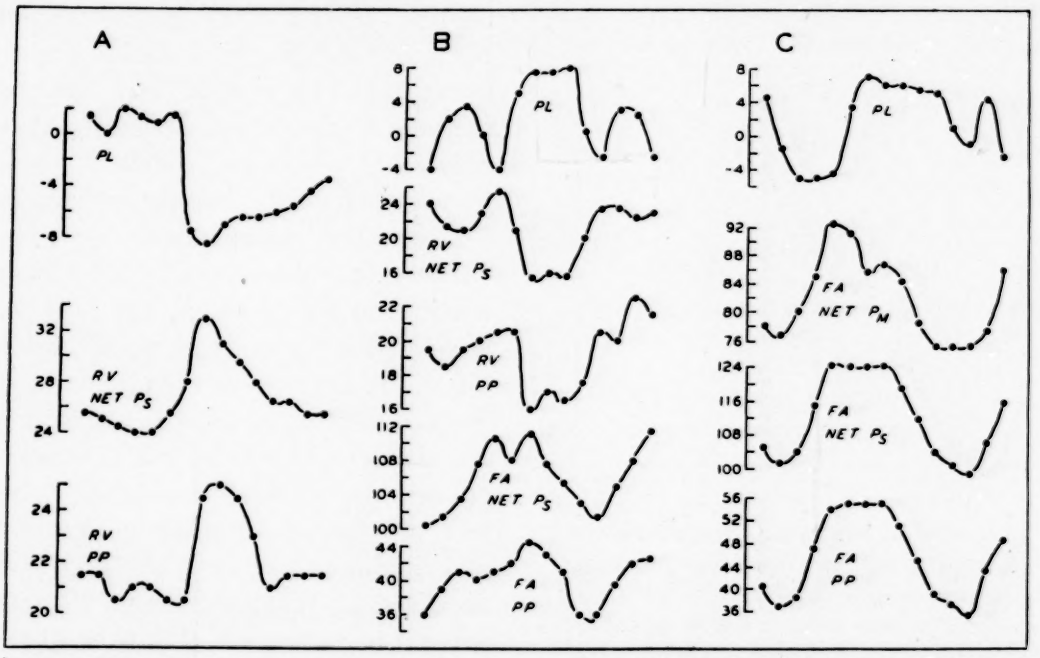

FIG. 16. *Correlation between pulse pressures and net pressures in right ventricle and femoral artery.* A, *intrapleural pressure* (PL), *net systolic pressure in right ventricle* (RV NET P_S), *and pulse pressure in right ventricle* (RV PP). *Pulse pressure is defined as difference between pressure at end of diastole and subsequent systolic pressure. Intrapleural pressure is not subtracted in determination of pulse pressure. The fifteen cardiac cycles were recorded during an expiration followed by a deep inspiration in patient No.* 45 (*same as in Figures* 12 *and* 14). *B, notations as in* A, *but in addition, net systolic pressure in femoral artery* (FA NET P_S) *and femoral arterial pulse pressure* (FA PP) *are plotted for same heart cycles. The arterial pulse pressure is the difference between the pressure at end of diastole and the subsequent systolic pressure. Intrapleural pressure is not subtracted in determination of femoral pulse pressure. Respiratory pattern during the fourteen beats shown consists of a forced expiration interposed between two moderately deep rhythmic respirations. Data are from patient No.* 48 (*same as in Figures* 1 *and* 8). C, *notations as in* B *except for addition of net mean pressure in femoral artery separately determined by planimetric integration for each cardiac cycle* (FA NET P_M). *Data are from patient No.* 49, *spontaneous pneumothorax, before aspiration. This graph shows that femoral pulse pressure variation is similar to net systolic pressure change and that both are well correlated with the variation of the net mean pressure.*

present in this case, the duration of the cardiac cycle was plotted in relation to the pressures in Figure 15. It is shown (1) that the net auricular pressure is lowest when the duration of the cycle is greatest. Therefore, factors other than time dominate the filling of the right heart in this case; (2) the higher net systolic pressures in the femoral artery are associated with the longer cycles; therefore, variations in the duration of the diastole may have been of some importance in determining the variation in filling of the left heart.

Since intrapleural pressure can be recorded only in a few selected cases, it is important to learn whether the pulse pressure variations, which can be measured independently of intrapleural pressure in all cases in which right ventricular and femoral arterial pressures are taken, are related to net pressure variations. There is evidence in Figures 16 and 17 to show that the correlations between the pulse pressures and net pressures are reasonably good. Therefore, pulse pressures may also be used as a qualitative index of stroke volume variations, provided there are no or only negligible changes in the pulmonary and systemic peripheral resistances.

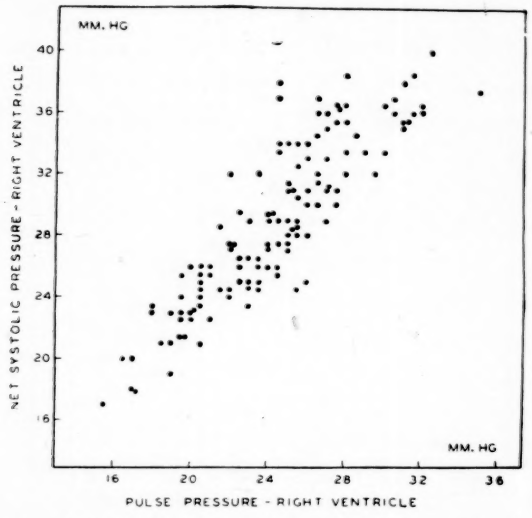

FIG. 17. *Correlation between pulse pressure and net systolic pressure in right ventricle. Data are from same cardiac cycles as in Figure* 11 (*patient No.* 46). *It is seen that pulse pressure variation may be used as a qualitative estimate of net pressure variation in cases in which intrapleural pressure is not measured.*

COMMENTS

The variations of blood pressure at the various sites in the circulatory system, as recorded in the tracings described above, depend directly on the changes of intrathoracic pressure during the respiratory cycle. The results in general confirm or are consistent with the data and interpretations of numerous investigations.

The inspiratory decrease of intrathoracic pressure, especially when inspiration is deeper than normal, directly enlarges the right auricle, as revealed by cinematography through a chest window in dogs.[13] This adequately explains the increased venous-auricular pressure gradient observed in the present study and in the experiments of Woodbury and Abreu,[14] as well as the increased venous flow toward the heart noted by Burton-Opitz.[15] Moreover, the cardiometric experiments of Boyd and Patras,[16] confirmed by Shuler et al.[17] show that the diastolic volume as well as the stroke volume of the combined ventricles increases during inspiration, provided the cardiometer is arranged to permit the pressure surrounding the heart to vary as the intrathoracic pressure. By placing markers along the interventricular septum, and taking motion pictures of the heart through a chest window, Shuler and his associates[17] were able to prove that the inspiratory dilatation of the combined ventricles in diastole is due entirely to enlargement of the right ventricle, and furthermore, that the left ventricular diastolic volume actually decreases. Thus, the decrease of intrathoracic pressure during inspiration acts to increase the filling of the right auricle and ventricle. These changes are in accord with the inspiratory increase in net right auricular and right ventricular pressures at the end of diastole observed by Wiggers in dogs[18,19] and in the present investigation. That the greater filling and stretch of the right ventricle results in increased output, which would be expected on the basis of Starling's law, was shown in the experiments of Shuler et al.[17] These data substantiate the interpretation that the inspiratory increase of net systolic pressure in the right ventricle, as described above, is due chiefly to the increase in stroke volume.

The inspiratory fall of intrathoracic pressure produces an increase in the capacity of the pulmonary vessels, to an extent more than sufficient to absorb the increase in right heart output.[20,13,21,22,23,24,25] As a result, an increment of blood is withheld from the left ventricle, and the volume of blood contained in the pulmonary vessels increases.

As a result of the lessened intrathoracic pressure in inspiration, the total pressure (i.e., pressure as referred to atmospheric pressure) in the pulmonary artery decreases.[19,26,27] Because of the increased right ventricular stroke volume, however, the *net* pulmonary arterial pressure rises.[26] Some of this rise might be attributed to an increase in resistance of the pulmonary vessels. However, studies on the isolated lung and heart-

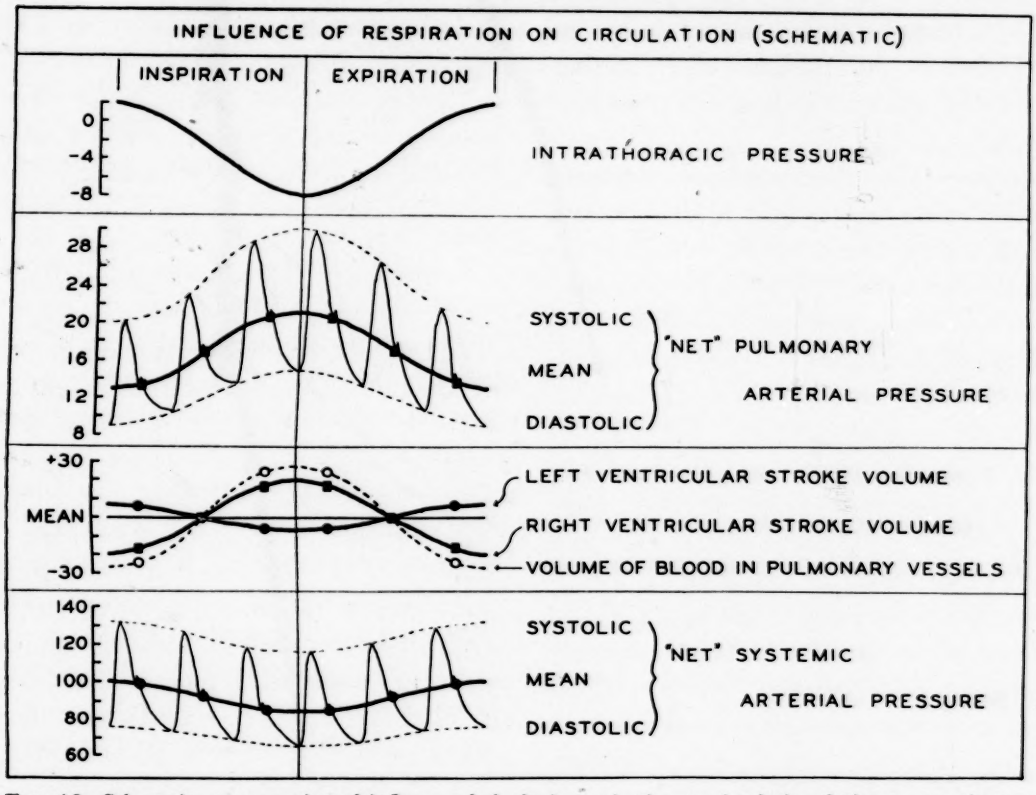

FIG. 18. *Schematic representation of influence of rhythmic respiration on circulation during one respiratory cycle of moderate depth. For simplicity's sake, inspiration and expiration have been assigned equal duration, all cardiac cycles are given the same duration, and the pulmonary and systemic peripheral resistances are assumed to remain constant during the respiratory cycle. The numerical values used are approximate estimates only. Intrathoracic pressure in mm. Hg is represented as an approximation of a sine curve. Solid square symbols in second row represent mean net pulmonary arterial pressure in mm. Hg, plotted as single values at mid-point of each cardiac cycle and connected by heavy curve. In third row, solid squares represent ml. per beat deviations of right ventricular stroke volume around the mean value, taken as 80 ml. The curve connecting these points is drawn identical to the curve of net pulmonary mean pressure, on the assumption that pulmonary vascular resistance remains constant. Similarly, solid circles in third row represent ml. per beat deviations of left ventricular stroke volume, and the curve connecting these points is drawn identical to the curve of net systemic mean pressure (bottom row) on the assumption that systemic peripheral resistance also remains constant. Since the two ventricular outputs vary in opposite directions during the respiratory cycle, the pulmonary blood volume will also vary. The magnitude of this variation is indicated by the open circles connected by the broken curve in third row, representing the algebraic difference between the right and left ventricular stroke volumes.*

In order to emphasize the fact that the net pulmonary pressures undergo proportionally greater variation than the net systemic pressures, the scales are drawn in a ratio of 5:1, corresponding approximately to the normal ratio of the mean pressures in the two arterial systems. Correspondingly, the right ventricular output is shown to vary by almost 20 ml. per beat, or ± about 25 per cent, around the mean of 80 ml., whereas the left ventricular output is considered to vary by only 5 or 6 ml. per beat, or ± about 7 per cent. It is not unlikely that the difference in magnitude of variation in the outputs of the two ventricles may actually be greater than shown in this schema (17, 20).

lung preparations show a decrease in resistance,[22,25] which would tend to diminish the rise in net pulmonary arterial pressures. In the intact anesthetized dog, Hamilton, Woodbury and Vogt[26] found that extreme inspiratory effort against an obstructed airway resulted in an increase in the net pulmonary arterial pressure, as well as an increase in the pulmonary arterio-venous pressure gradient. Since there is a considerable increase of outflow from the right ventricle in this situation, it is likely that most

of the arterio-venous gradient increase must be attributed to an increased flow rather than to an increase in pulmonary vascular resistance.

As noted above, the increased capacity of the pulmonary vessels during inspiration, usually exceeding the increase of right heart output, decreases the left ventricular output. The aortic pressure, therefore, falls because of the direct effect of lessened intrathoracic pressure on the thoracic aorta,[7,28] and because of the indirect effect of decreased left ventricular output. Hamilton believes that in normal quiet breathing only the direct effect is important.[29] Dupee and Johnson[20] have emphasized that the respiratory variations of output are much less in the left ventricle than in the right, largely because of the simultaneous variation in the intervening pulmonary blood volume. In this sense, the lung vessels may be considered a buffer between the right and left ventricles, promoting a more constant output from the left heart.

The preceding discussion has been confined mainly to the inspiratory phase. During expiration the opposite changes take place.

The operation of the several factors in rhythmic respiration of moderate depth are schematically integrated in Figure 18. Direct application of this simple schema to clinical situations requires some caution, especially in those cases in which significant changes in pulmonary resistance might occur, as, for example, in intermittent positive pressure breathing. Furthermore, the pattern will be modified considerably if there are changes in heart rate, where variation in the duration of diastole adds another variable. Finally, it is obvious that the basic pattern shown in Figure 18 may be altered by *changes* in the following: depth of respiration, relative duration of inspiration and expiration, respiratory rate, kind of respiration, i.e., "abdominal" or "thoracic," pulmonary vascular capacity as a result of disease or therapy, distensibility of the ventricles in diastole (e.g., as in pericardial disease), venous return (as in peripheral circulatory failure and cardiac failure), to mention only some of the possible factors.

SUMMARY AND CONCLUSIONS

1. A study has been made of the influence of various forms of respiration on the pressures in the right auricle, right ventricle, central veins, antecubital vein and femoral artery in normal subjects and in patients with chronic pulmonary or cardiac disease. Intrapleural pressure, in addition, was recorded in four cases of pulmonary tuberculosis with recently induced therapeutic pneumothorax and normal circulation.

2. Representative records and data from eighteen cases are described and interpreted.

3. In quiet breathing there are only very slight rhythmic variations in the blood pressures.

4. In rhythmic breathing of moderately increased depth, inspiration leads to the following: (1) an increase in the peripheral vein—right auricular pressure gradient; (2) an increase in the *net* pressure in the right ventricle at the end of diastole; i.e., an increase in the difference between the pressure in the filled ventricle and that in the surrounding intrathoracic space; (3) an increase in the *net* pressure in the right ventricle during systole, which is interpreted as indicating an increase in the right ventricular stroke volume during inspiration; and (4) a decrease, which is proportionally smaller, in the *net* systolic pressure in the systemic arteries, which is interpreted as indicating a decrease in the left ventricular stroke volume.

5. Opposite changes take place during expiration.

6. Modifications of this basic pattern are described for sustained inspiration and

expiration, for cough, and for the Valsalva and Mueller experiments, in which forced expiration and inspiration, respectively, are performed against the closed glottis.

7. Modifications of the right auricular pressure curves due to deep respiration are illustrated by records from normal subjects and from patients in congestive heart failure.

8. The essential features of Starling's law of the heart are demonstrated under physiological conditions in the case of the right ventricle in patients whose intrapleural pressure was recorded. It is shown that the greater the net initial pressure, the greater the net pressure developed in the subsequent contraction.

9. Evidence is presented to show that the variation of the pulse pressure in the right ventricle (systolic pressure minus the pressure at the end of diastole of the preceding cycle) and in the systemic arteries is qualitatively similar to the corresponding net pressure variations. It is possible, therefore, in the absence of the intrapleural pressure record, to estimate qualitatively the variation of the right and left ventricular stroke volumes from the right ventricular and femoral arterial pressure curves alone, if there is no change in heart rate and assuming negligible change in vascular resistance.

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Clinical Syndrome of Potassium Intoxication*†

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In developing an adequate perfusate for the isolated mammalian heart, Ringer[1] demonstrated that either too low or too high a concentration of serum potassium would interfere with muscle contraction. These opposite effects of potassium occur *in vivo* as well as *in vitro*. Striate muscle paralysis may be associated with low serum potassium following injection of desoxycorticosterone,[2] or may be observed clinically in uremia with a high serum potassium.[3] In this report, we are concerned with the effects of high serum potassium on cardiac and skeletal musculature.

Accumulation of potassium in the human body is lethal when it reaches a level in the serum of about 10 to 10.5 milliequivalents/l. (39 to 41 mg. per 100 cc.) due to its effect on the myocardium. This is substantiated by a previous report in which patients developed a typical sequence of electrocardiographic changes ending in cardiac standstill.[4] The terminal character of the disease in these patients, however, together with the retention of many other metabolic products, leaves certain questions unanswered. Is the interference with heart muscle contraction purely a function of accumulation of the potassium ion, and is the dysfunction reversible when electrolyte equilibrium is regained? Is striate muscle paralysis contingent on the same factors which produce cardiac standstill? Our two cases illustrate the rapid onset of widespread muscle paralysis and specific electrocardiographic changes due to accumulation of potassium and the reversibility of both under therapy.

CASE REPORTS

CASE 1. J. D., (M67842), a fifty-nine-year-old printer, was admitted to the Peter Bent Brigham Hospital on January 31, 1945, for study of jaundice which had been continuously present since the age of twelve. There was no family history of jaundice. For twenty-five years he had handled printing type and had used a cleaner known as "Carbopeptone." Over the three years prior to admission, he lost 14 kg., and for nine months he experienced progressive malaise and exertional dyspnea. There was also nocturia two or three times nightly.

Physical examination revealed the temperature to be 98.6°F., pulse 68, blood pressure 114/80 mm. Hg., respiration 20. The patient, a thin, poorly nourished individual of small stature, was lying quietly in bed in no acute distress. He seemed somewhat drowsy and responded poorly to questions. His skin was icteric, smooth and dry, with some loss of elasticity. Fingernails and lips appeared cyanotic, especially when cold. The chest was clear to percussion and auscultation. The heart border was inside the midclavicular line on the left by percussion, and there was a grade 1 systolic murmur at the apex. The liver was

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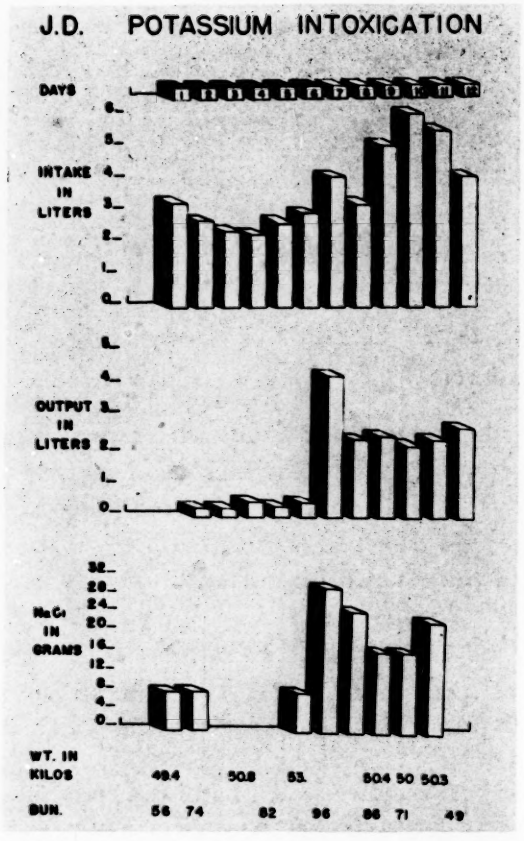

FIG. 1. *Case* I. *The fluid balance sheet of Case* I *may be divided into two parts:* A, *first six days of oliguria with progressive azotemia.* B, *the diuretic period beginning with the seventh hospital day. It was at that time that potassium intoxication developed, and that intensive sodium chloride therapy was instituted.*

palpable one fingerbreadth below the right costal margin. The edge was sharp and nontender. The spleen was not felt. Reflexes were of normal intensity. There was no peripheral edema. Feet were bluish-purple in color and were colder than the remainder of the body, which was cool.

The blood Hinton test was negative; red blood count, 5,400,000 per cu. mm., hemoglobin 17.6 Gm. per cent, hematocrit 54 per cent, white blood count 15,100 per cu. mm. with 54 per cent neutrophils, 30 per cent lymphocytes, 10 per cent monocytes, 5 per cent eosinophils, 1 per cent basophils; reticulocytes were 0.9 per cent. Fragility of the red cells to hypotonic saline was normal. Urinary urobilinogen was not increased, and the fecal urobilinogen was 68 mg. per day (Watson's method).* Serum bilirubin levels varied between 0.6 and 1.0 mg. direct reacting and 7 to 10 mg. of total bilirubin (method of Evelyn and Malloy).* The stool contained no occult blood or excess of fat. Urine specific gravity on admission was 1.019 with no protein, and the sediment contained a rare white blood cell and hyaline cast. Blood urea nitrogen on the second hospital day (February 1) was 60 mg. per cent. Alkaline phosphatase was 3.0 Bodansky units and serum amylase 106 mg. per cent. Intravenous glucose tolerance test showed a retarded fall to normal and no hypoglycemic phase. Bromsulfalein test (5 mg. per kg.) showed 40 per cent retention in thirty minutes. Prothrombin time was prolonged (control 35 seconds, patient 55 seconds). Blood cultures were negative on four occasions, and another showed an alpha streptococcus, thought to be a contaminant. Stool culture was negative as were enteric agglutinations. Brucella skin test was negative. *X*-ray of the gallbladder showed good concentration of dye and a normally functioning gallbladder. Gastrointestinal series and chest films were normal.

On the evening of admission, the patient was given 5 Gm. of Priodax by mouth. Four hours later nausea, vomiting and diarrhea began. The following day, the blood pressure fell to 60/0 mm. Hg., and the extremities were cold and cyanotic. After administration of plasma, glucose and saline, he recovered temporarily from shock but during the following seven days, despite a total intake of 17 liters of fluid containing 27 Gm. of salt, diarrhea and hypotension were intermittently present. The total urine output was only 1.5 liters. (Fig. 1.) During this time the blood urea nitrogen rose to 96 mg. per cent, and carbon dioxide fell to 12.5 milliequivalents per liter. To counteract acidosis, 44 cc. of molar sodium lactate, 1,000 cc. of 10 per cent glucose, and 1,000 cc. of 5 per cent glucose in saline were given intravenously the morning of the seventh day. The patient appeared tired but mentally clear. At 7:15 P.M. it was noticed that he talked thickly and was unable to swallow water. During the next two hours, he became progressively paralyzed. At 9 P.M. he was unable to raise his arms or hands

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* MALLOY, H. T. and EVELYN, K. A. *J. Biol. Chem.*, 119: 481, 1937.

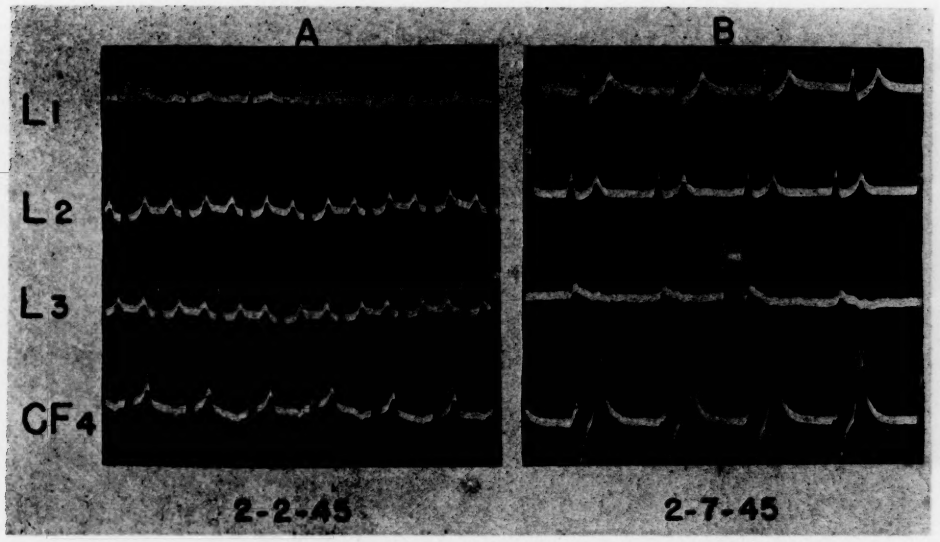

FIG. 2. *Case* I. A, *tracing taken on the second hospital day provides a normal base line with which to compare subsequent changes;* B, *tracing taken five days later at* 9:15 P.M., *two hours after the onset of paralysis. The P wave has disappeared except for a single deflection in lead* I. *The R wave is decreased in amplitude in leads* II *and* III. *An S wave has appeared in lead* I. *QRS and T complexes show spreading. The T wave is taller in leads* I *and* II, *and particularly in lead* IV.

with the exception of his fingers which he could flex. His legs were immobile except for the toes which could be moved slightly. Respirations were shallow and labored with a rate of 36 per minute. His facial muscles were weak and he was unable to lift his head off the pillow. Reflexes were completely absent in the arms and legs. Pain sensation was intact. Vibratory sense was lost from the iliac crests downward, and position sense was absent in the feet. His arms and legs were warm and dry and arterial pulsations were good. He complained of a feeling of numbness in his hands. The lungs were clear. The apical impulse of the heart was palpated outside the nipple line. The sounds were mushy and the apical systolic murmur had increased slightly in intensity. There were slight pauses in the heart rhythm. An electrocardiogram, which was taken at 9:15 P.M., showed the typical changes associated with potassium intoxication. (Fig. 2B.)

Accordingly, treatment was started at 9:30 P.M. One Gm. of calcium gluconate was injected intravenously in a ten-minute period. This seemed to increase the rate of the heart only slightly. During the first fifteen minutes, 500 cc. of isotonic sodium chloride were given intravenously. At the end of this time, he was able to move his hands. Heart sounds improved in quality, and the electrocardiographic changes of potassium were already regressing. (Fig. 3B.)

Within an hour his paralysis had disappeared and respirations became easier. With return of muscle function, he developed a positive Chvostek's sign and twitching of large groups of muscle fibers over his entire body, which lasted several hours. Reflexes became hyperactive. During the night he was given a total of 2.25 Gm. of calcium chloride and gluconate, 31.5 Gm. of sodium chloride and 4,200 cc. of water. His urinary output over the same time was 4,300 cc. Blood chemistries during this period showed high concentrations of serum potassium, and low serum sodium values.* These were correlated with serial electrocardiograms. (Figs. 6 and 7.) At the onset of paralysis, serum calcium was 5.3 milliequivalents/l. (10.6 mg. per 100 cc.), rising to 6.3 milliequivalents subsequent to treatment. The initial serum chloride of 88 milliequivalents/l (312 mg. per 100 cc.) also rose by the following morning to 97 milliequivalents/l. (344 mg. per 100 cc.). The test for urinary urobilinogen was negative after the attack.

* Specimens were collected under oil and serum separated at once. Sodium was determined according to the method of Consolazio, W. V., and Dill, D. B. (*J. Biol. Chem.*, 137: 587, 1941) and potassium according to the method of Consolazio, W. V. and Talbott, J. H. (*J. Biol. Chem.*, 126: 55, 1938).

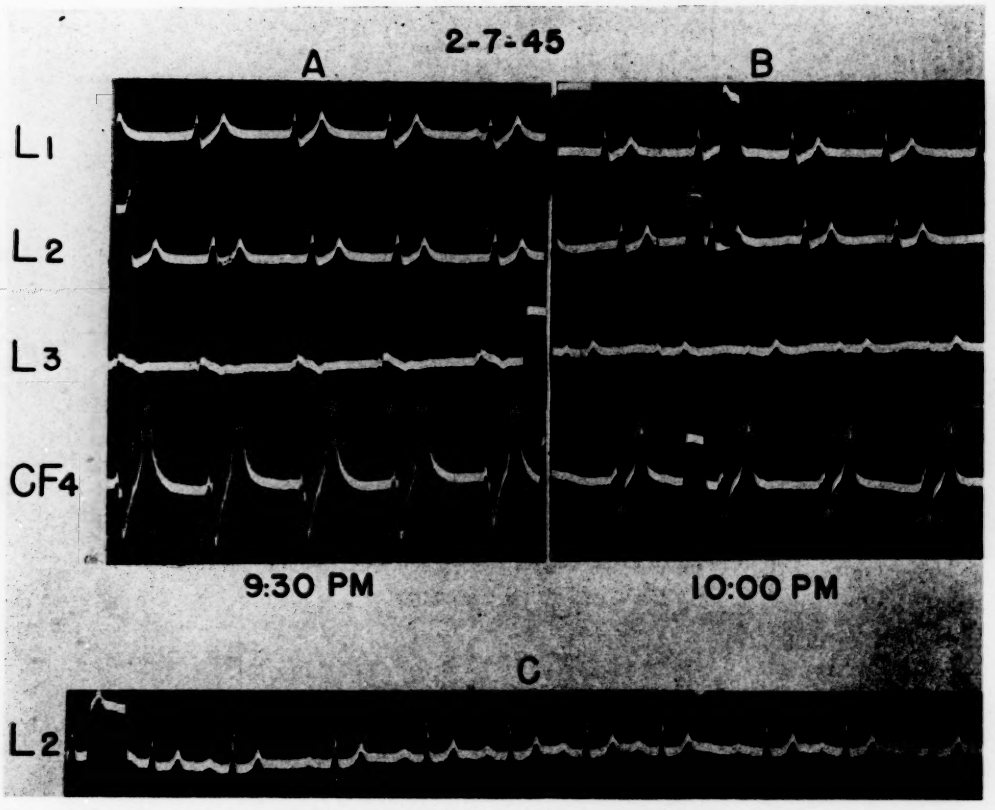

FIG. 3. *Case* I. A, *tracings at* 9:30 P.M. *just before treatment was started show progression of changes described in Figure* 2B. *Other than a single P wave in lead* I, *there is no evidence of auricular contraction.* B, *tracing at* 10:00 P.M. *was taken after approximately* 1 *liter of sodium chloride and* 2 *Gm. of calcium salt had been given, and after recovery from the paralysis had occurred. There is less spread of the QRS and T complexes, and a decrease in amplitude of T waves.* C, *tracing at* 10:15 P.M., *forty-five minutes after therapy was begun, shows the reappearance of P waves in lead* II. *They vary in size and are broader and flatter than in the control tracing. PR interval is* 0.22–0.24 *seconds.*

During the following week his weight fell from 53 to 49 kg. There was a fall in the blood urea nitrogen to less than 40 mg. per cent. Serum chloride was maintained between 95 and 100 milliequivalents/l. by the daily administration of 15 to 25 Gm. of sodium chloride. Desoxycorticosterone, 5 mg. per day, without salt, resulted in a fall of the chloride to 90 milliequivalents/l. and a 2 kg. weight loss over a period of ten days.

Throughout the remainder of his hospital course, the blood urea nitrogen was stabilized at approximately 20 mg. per cent; the urine never had more than 1+ albumin, and its specific gravity ranged between 1.006 and 1.015. Eosinophilia increased to 25 per cent. Fever as high as 103°F. was present and did not respond to penicillin. Food intake was poor, jaundice increased, and a cholemic stupor ensued on the seventh hospital day. On the seventy-third day, the respiratory rate accelerated to 48 per minute, heart sounds became faint and the pulse unobtainable. Permission for autopsy was not granted.

Comment. The patient's jaundice would seem to be typical of that described as constitutional hepatic dysfunction or familial non-hemolytic jaundice. This syndrome represents a fairly specific inability of the liver to excrete bilirubin and is generally considered to have a benign prognosis by most authors[5,6,7] with the exception of Mogena.[8] This patient, however, after some forty-seven years of jaundice showed obvious evidence of hepatic insufficiency. Serum albumin fell to 1.9 Gm. per cent, prothrombin time was prolonged, there was 40 per

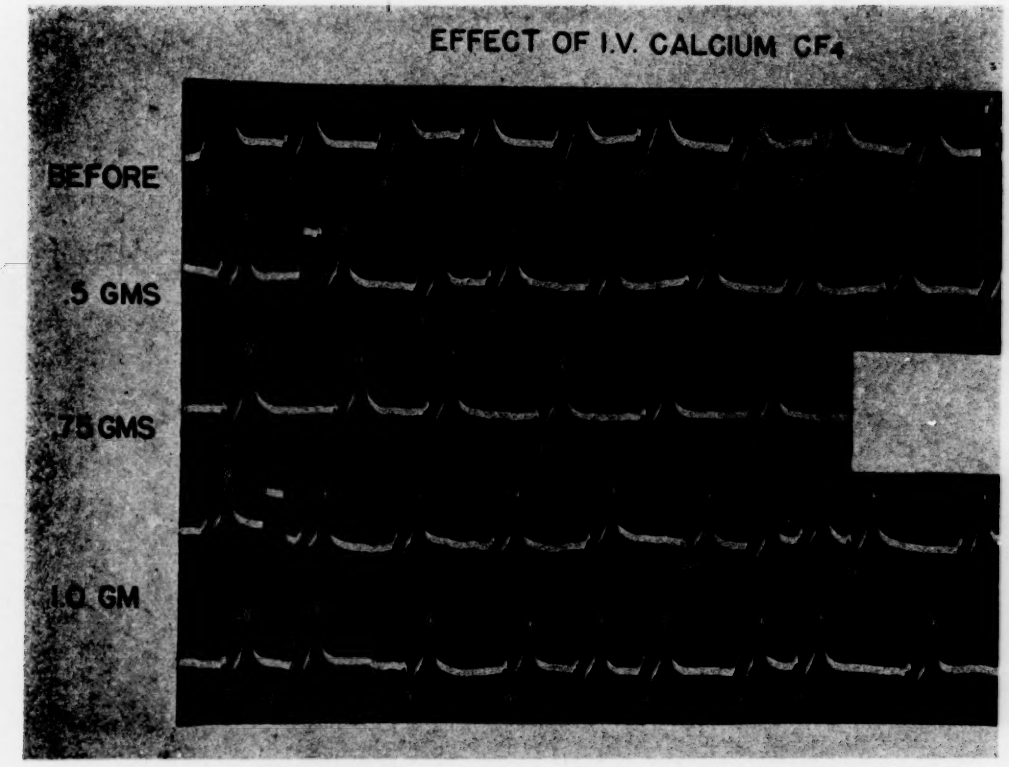

FIG. 4. *Case* I. *Precordial lead taken from* 9:30 *to* 9:40 P.M. *while* 1 *Gm. of calcium chloride was injected intravenously, showing increase in rhythmicity, slight decrease in spread of QRS and T, and less elevation of the T wave.*

cent bromsulfalein retention, a macrocytic anemia and increasing bilirubinemia. Cholemic stupor was present during the week before his death.

The rôle of Priodax in precipitating the paralytic episode is not clear. Local gastrointestinal irritation with associated nausea and vomiting progressing to shock undoubtedly did throw already damaged kidneys into severe failure. On the other hand, about 80 per cent of Priodax is excreted through normal kidneys in forty-eight to seventy-two hours,[9] and in the face of severe oliguria it is possible that renal tubular lesions similar to those observed experimentally in the cat may have been produced.[10]

Figure 1 illustrates the fluid and salt imbalance during the first week, which laid the scene for potassium intoxication. During the first week, the patient appeared dehydrated and the high hematocrit was evidence of hemoconcentration. Despite this, there was an actual gain in weight of 3 to 6 kilograms. This ambiguity can be explained by assuming extracellular dehydration and intracellular edema. Serum sodium was also depleted. To counteract the sodium deficiency and maintain osmotic equilibrium between these two fluid compartments, two compensatory mechanisms apparently operated: (1) a shift of water intracellularly and (2) loss of potassium from the cells into extracellular fluids. This same fluid and electrolyte shift has been observed in adrenal insufficiency.[11]

On the seventh day a critical period was reached. The patient abruptly developed widespread muscle paralysis and involvement of the heart as well. The effect of calcium and sodium chloride therapy is demonstrated in electrocardiographic tracings in Figures 3, 4, 5, 6 and 7. The diuresis following therapy resulted in a fall of blood

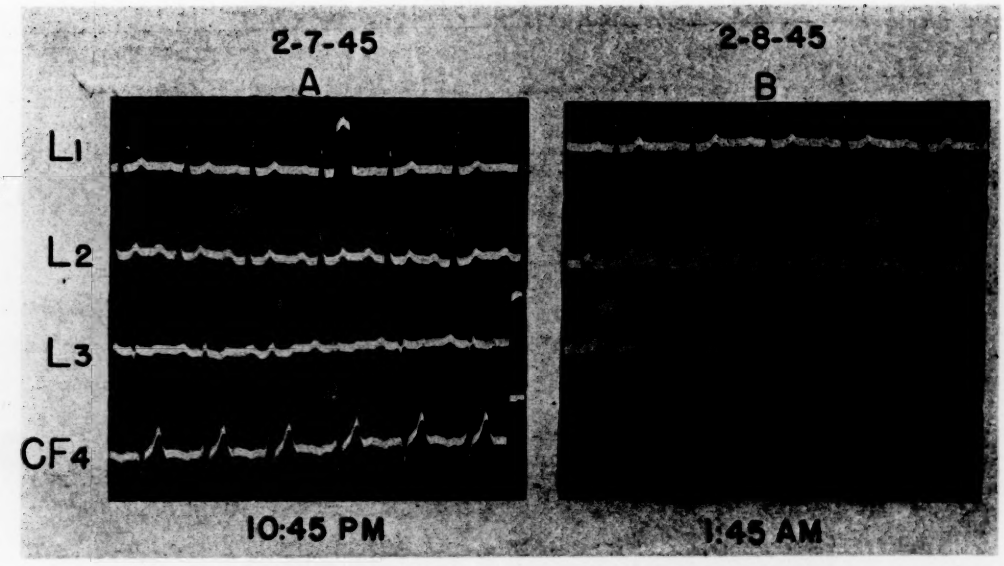

FIG. 5. Case I. A, *One hour after beginning treatment. P waves have returned. PR interval* 0.20 *as compared with control of* 0.16 *seconds. The S wave in lead* I *has disappeared and T waves are returning to normal.* B, *four hours after treatment began.* T_3 *is now upright and other changes have reverted to normal.*

urea nitrogen to 20 mg. per cent, a fall in weight from 53 to 50 kilograms, and a fall in hematocrit to 36 per cent. These data would indicate that the fluid diuresed from the intracellular compartment, for at the same time the extracellular fluid was increasing in volume as indicated by a fall in hematocrit and increase in blood volume.

The patient's weakness, hemoconcentration, hypotension, tendency to develop shock, potassium intoxication and large salt requirements in later days of hospitalization all pointed toward an uncontrolled loss of sodium chloride in the urine. Desoxycorticosterone was ineffective in checking the salt loss, thus excluding Addison's disease and placing the tubular lesion on an organic basis, analogous to the cases of salt-losing nephritis reported by Thorn, Koepf and Clinton.[12]

CASE II. J. O'N. (M69498), a forty-two-year-old married contractor, was admitted to the Peter Bent Brigham Hospital November 18, 1945, because of nausea, vomiting, and blurring of vision of one month's duration. His general health had been excellent until sixteen months prior to entry when he complained of sore back and leg muscles. Studies at that time were said to have revealed albuminuria and prostatitis but no hypertension. Ten months later he developed severe occipital headaches relieved by aspirin, and his systolic blood pressure was found to be "over 200 mm. Hg." Morning nausea and vomiting, progressive malaise, and anorexia were soon to follow, and a month before entry he was digitalized because of nocturnal dyspnea. During this month he had some muscle twitchings and insomnia. His weight during the preceding year had fallen from 210 to 175 pounds.

Physical examination revealed his temperature to be 98.6°F., pulse 84, respirations 20, and blood pressure 170/118 mm. Hg. The patient was a husky, apprehensive, middle-aged male. His skin was pale, dry, warm, with a fine punctate erythema over the abdomen. There was no cyanosis or edema. The fundi were pale with tortuous vessels, hemorrhages and exudates in the right eye, and bilateral papilledema. A few moist scattered râles were heard through both lung fields. The heart was enlarged with a grade 2 murmur heard over the precordium. A_2 was louder than P_2, and the rhythm was regular. The liver extended three fingerbreadths below the costal margin. Rectal examination revealed several hemorrhoids and a prostate enlarged to about twice normal size, boggy in

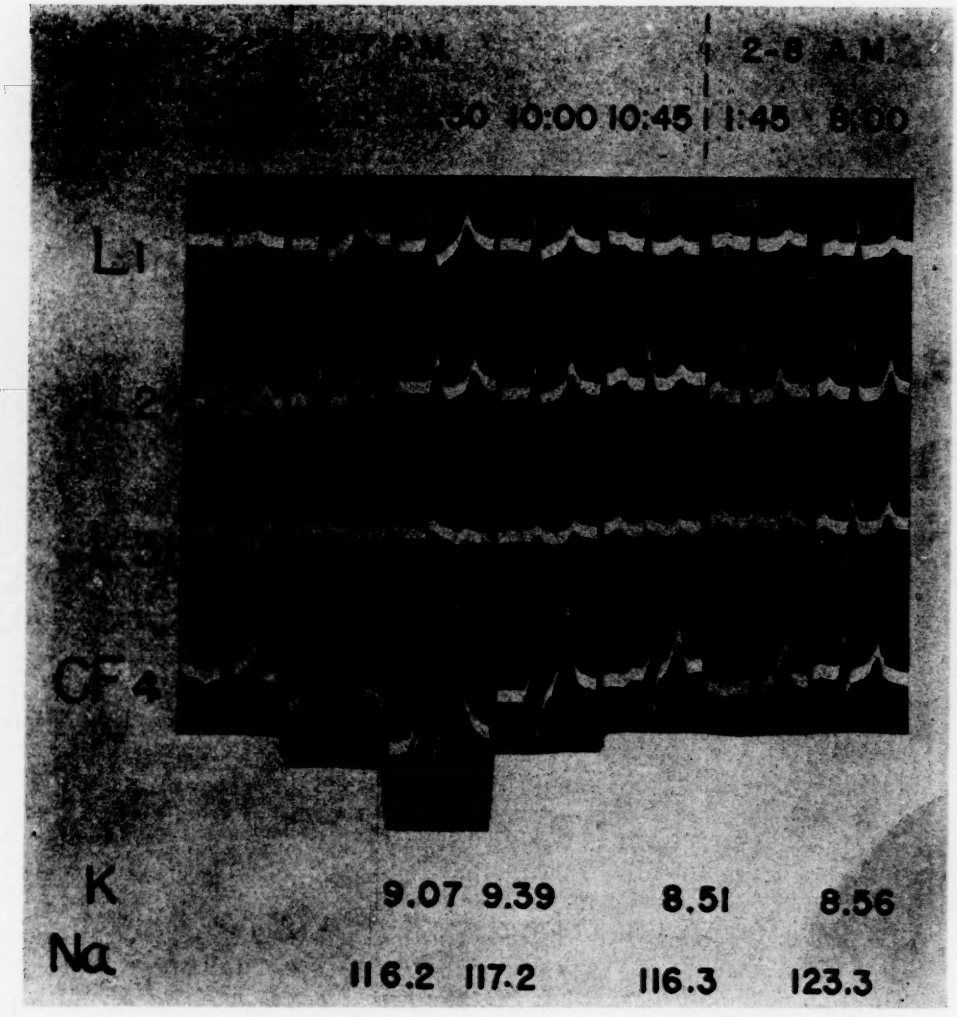

FIG. 6. *Case* 1. *A composite of routine leads taken during the episode of potassium intoxication. First tracing represents control taken five days previously. Second and third tracings were taken before treatment was instituted. Subsequent four tracings were taken during treatment and show the return of complexes to a state of normalcy. The associated serum potassium and sodium levels listed, expressed as milliequivalents/l.* (*To transpose to mg./100 cc. multiply potassium by* 3.91 *and sodium by 2.3.*)

consistency but with a well defined groove. Neurological examination was physiological.

The blood Hinton test was negative. Urine was light yellow in color with a specific gravity of 1.010. There was a 2+ protein, and the centrifuged sediment showed 20 to 30 red cells, 2 to 6 white cells per high power field, but no casts. Subsequent urinalyses revealed a low fixed specific gravity and occasional granular casts. Hemoglobin content of the blood was 5.2 Gm. per cent, red count 1,920,000 per cu. mm. and hematocrit 17 per cent. White blood count was 6,200 per cu. mm. with 66 per cent neutrophils, 21 per cent lymphocytes, 7 per cent monocytes, 4 per cent eosinophils and 2 per cent basophils. On admission, blood chemistries showed a blood urea nitrogen of 110 mg. per cent, a total protein of 5.2 Gm. per cent, a fasting blood sugar of 112 mg. per cent, a carbon dioxide combining capacity of 14 milliequivalents/l., and serum chlorides of 103 milliequivalents/l. (365 mg. per 100 cc.). Calcium was 3.4 milliequivalents/l. (6.8 mg. per 100 cc.) and phosphorus 4.2 milliequivalents/l. (13 mg. per 100 cc.). Three stool specimens were 1+ guaiac. Phenolsulfonphthalein excretion in two hours was negligible. *X*-ray of the chest revealed the heart to be about 24 per cent above

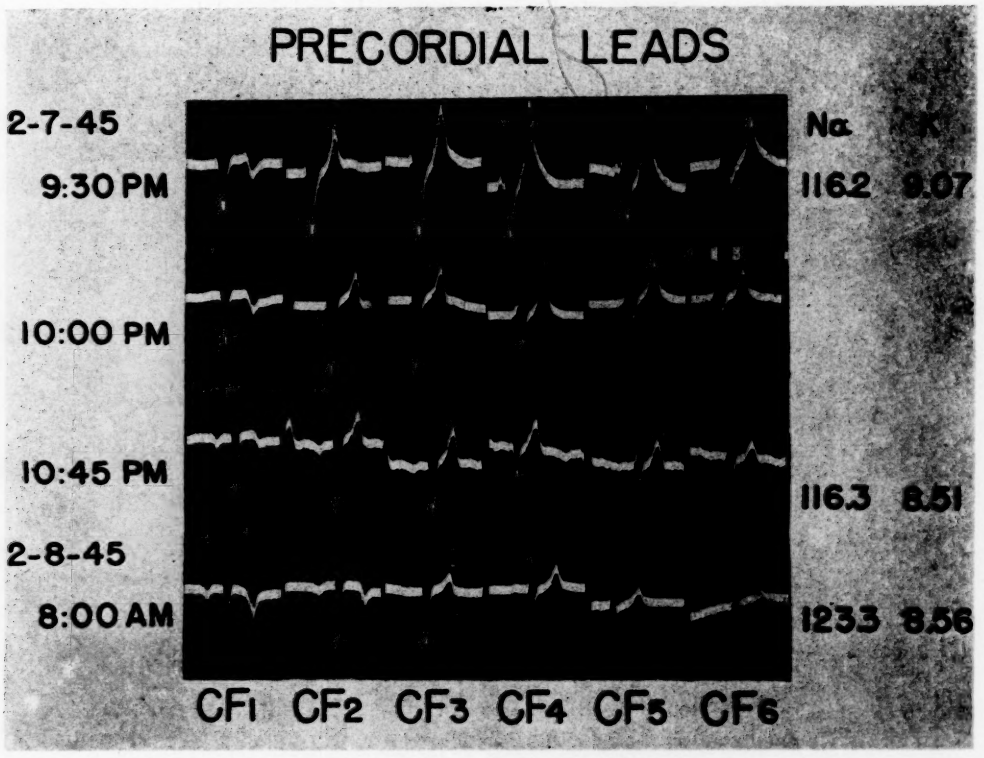

FIG. 7. *Case* 1. *Multiple precordial leads taken with the negative electrode on the left leg and the positive electrode on the precordium. First series is before treatment and the subsequent three are during treatment. The spread of QRST and elevation of T is evident in all leads from the left side of the chest. Sodium and potassium expressed as milliequivalents/l.*

average in size by height-weight ratio and there was definite pulmonary congestion. Electrocardiogram on the third hospital day was normal except for moderate left axis deviation.

On the second hospital day the patient was placed on an alkaline-ash diet containing 60 Gm. of protein and 3 Gm. of salt. Fluid intake averaged 2,000 cc. per day and urine output 750 cc., while his weight remained constant at 80 to 81 kg. He became progressively more apprehensive and was bothered by nausea and vomiting. On the fifth day a precordial friction rub was heard for the first time. On the morning of the sixth day an electrocardiogram was taken (Fig. 8B) which showed the early T wave changes characteristic of a high serum potassium. During the day he grew weaker. At 11:00 P.M. he complained for the first time of numbness of the legs. Examination at 1:00 A.M. revealed the precordial friction rub previously noted. The heart sounds were not as hyperactive as they had been previously. Electrocardiogram at this time showed well advanced potassium effect with auricular standstill and marked T wave alterations. (Fig. 8C.) Serum potassium at this time was 10.2 milliequivalents/l. and sodium 130.0 milliequivalents/l.

One hour later, at 2:00 A.M., there was a complete flaccid quadriplegia with involvement of the neck muscles so that the patient was unable to support his head. There was some movement of facial muscles. Reflexes in the extremities were absent; on direct percussion the muscles of the arm could be made to contract. Upon auscultation the heart sounds were much fainter than they had been one hour previously, and each contraction seemed prolonged as if the heart were contracting very slowly. The rhythm was irregular and there was a marked bradycardia. Electrocardiograms at this time showed an extreme conduction defect. (Fig. 9.) Respirations were fairly strong, but the pulse was small and the extremities were cold. At this point the patient became unresponsive.

Three per cent sodium chloride was started intravenously at 2:35 A.M. By 3:10 A.M., a total

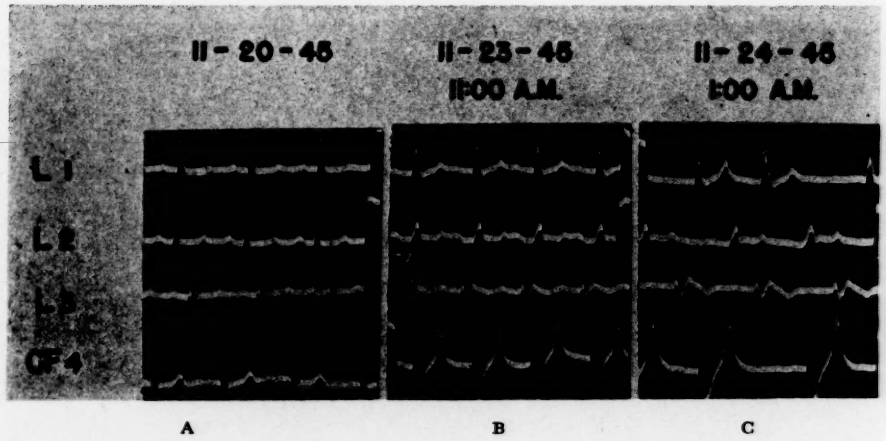

FIG. 8. *Case* II. A, *tracing taken on* 11-20-45, *three days before onset of paralysis shows only left axis deviation and a normal PR interval of* 0.16. B, *tracing taken on* 11-23-45, *approximately twelve hours before onset of weakness, shows PR interval of* 0.20 *with spreading of the P waves, spreading of the QRS complex and T wave elevation, particularly in lead* IV. C, *P waves have practically disappeared. There is irregularity of rhythm, further spread of the QRS and progressive T wave elevation in lead* IV.

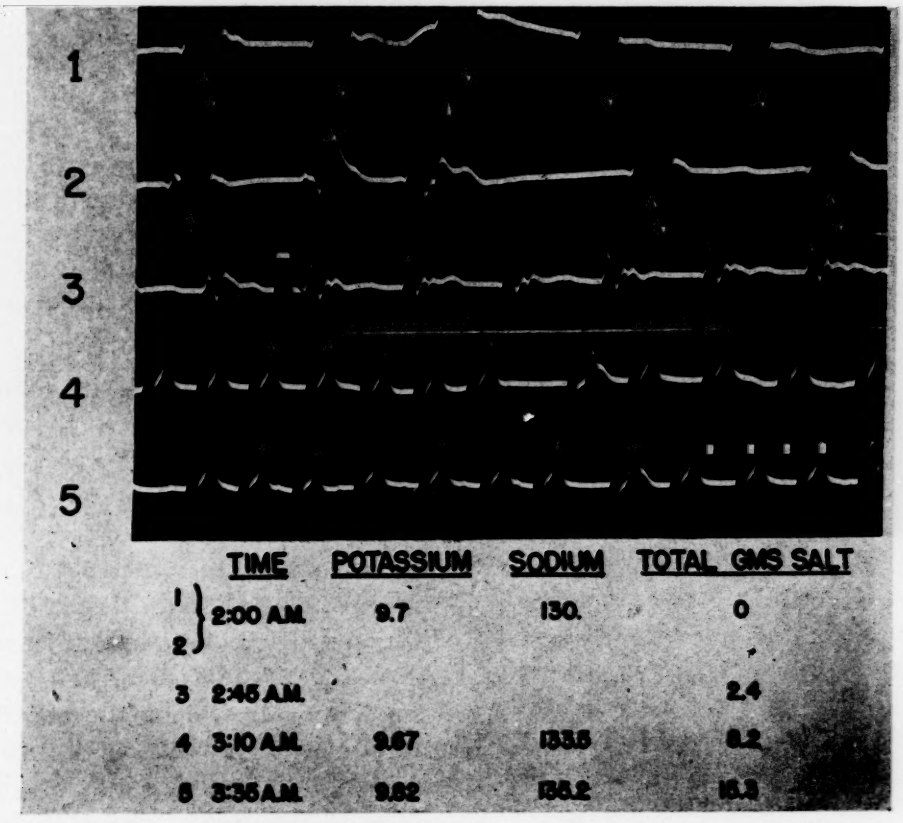

FIG. 9. *Case* II. *Tracings are all* CF_4 *and the electrocardiogram is correlated with serum sodium and potassium levels and intravenous salt administration. At* 2:00 A.M. *rhythm was irregular, rate about* 30 *per minute, complex is variable with a marked conduction block. At* 2:45 A.M. *following injection of* 3 *per cent saline, rate had increased and block in QRST complex decreased. By* 3:10 A.M. *complexes were comparable to those taken before onset of paralysis, and by* 3.35 A.M. *P waves were again discernible.*

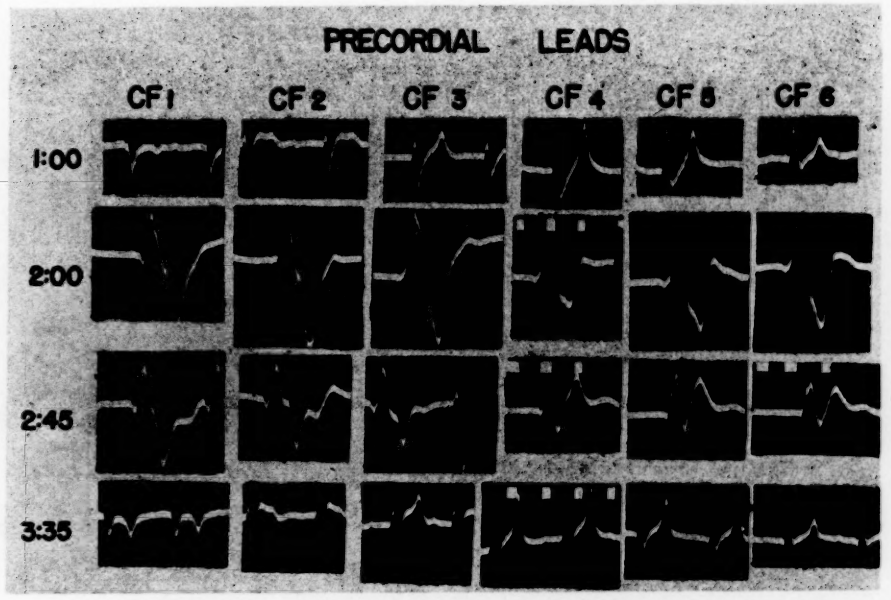

FIG. 10. *Case* II. *Multiple precordial leads show the progression of potassium effect between* 1:00 *and* 2:00 A.M. *and its regression after injection of sodium chloride. The block in leads from left and right precordium appear of the same nature, representing a generalized conduction impairment throughout the heart.*

of 410 cc. had been given, and the patient began to rouse from his moribund state. His head moved slightly and his right arm jerked. Within five minutes his reflexes returned and he was able to move fingers and toes. His pulse became stronger and his blood pressure, which a few minutes previously had been unobtainable, was 120/80 mm. Hg. The patient moved his hands back and forth in front of his eyes as if amazed at being able to move them. He appeared well oriented and remembered clearly his previous paralytic state. His heart sounds at this point had become louder and more crisp. An electrocardiogram at this time showed regression of the changes attributed to potassium. (Figs. 9 and 10.)

At 5:00 A.M. there was return of weakness; the patient became drowsy and complained of "blacking out." His heart rate had dropped to between 5 and 15 per minute, and the heart sounds were prolonged and distant. Extremities were cold. Respirations were grunting. During the next twenty-five minutes 370 cc. of 3 per cent saline were administered intravenously, and again the patient became alert mentally, reflexes and motor power returned, heart rate increased, and blood pressure was obtainable. Again the improvement in quality of heart sounds could be correlated with improvement in conduction in the electrocardiogram. (Figs. 11, 12 and 13.) For some forty minutes the patient remained fairly alert, but thereafter he became unconscious with marked bradycardia and depression of respirations. Finally death from cardiac standstill occurred at 7:10 A.M.

Comment. The clinical course of this patient is fairly typical of the average patient with severe renal disease, at least up to the last twenty-four hours of life. Indeed, the mechanism involved in his death might have gone unnoticed had it not been for the electrocardiogram taken on the last day which showed changes consistent with high serum potassium. (Fig. 8B.) On two separate occasions during the night the patient was moribund with electrocardiographic evidence of advanced potassium intoxication of the heart, and each time it was possible to reverse the process by administration of sodium chloride. It is interesting that this improvement was effected temporarily by salt administration in spite of the

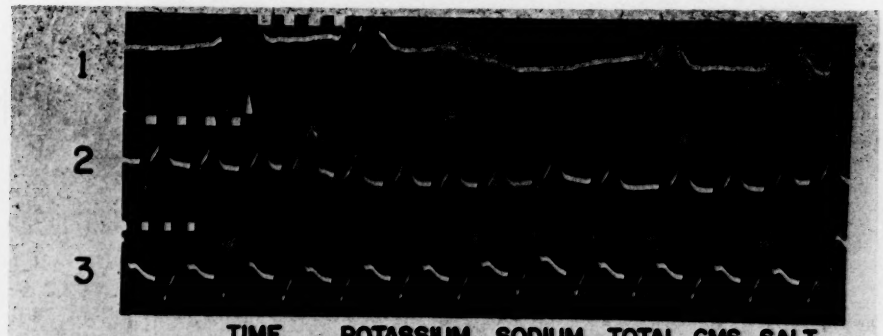

FIG. 11.

	TIME	POTASSIUM	SODIUM	TOTAL GMS SALT
1	5:02			15.3
2	5:25	10.1	139.0	26.4
3	6:10			34.5

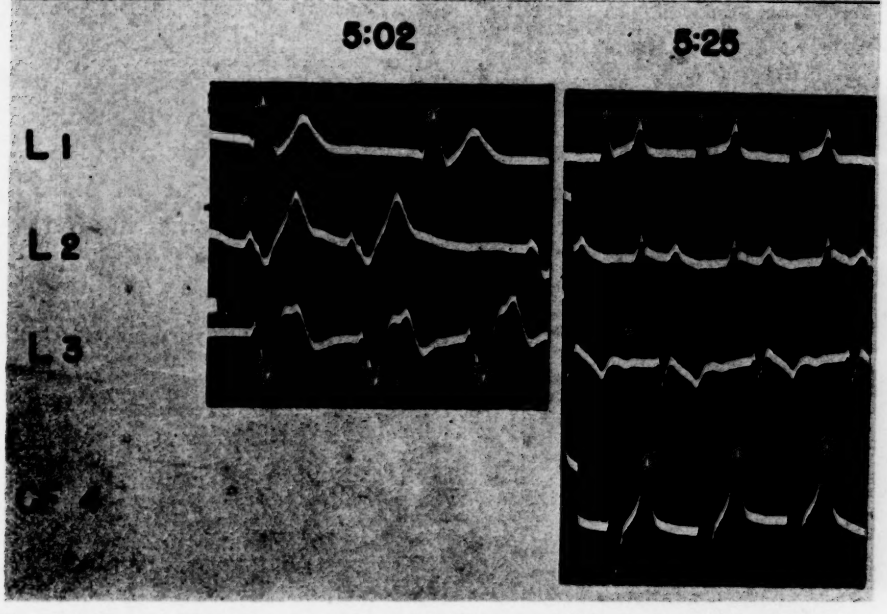

FIG. 12.

FIG. 11. *Case* II. *All tracings were taken with* CF_4 *precordial leads showing the marked impairment and disorganization of ventricular conduction and bradycardia which again responded to intravenous saline. By* 6:10 A.M., *however, the changes progressed despite further therapy.*

FIG. 12. *Case* II. *Limb leads before and after intravenous salt administration showing the reversion towards normal with marked decrease in the conduction block of the QRST complex.*

fact that the serum potassium level remained fairly constant.

There was such close correlation of auscultatory findings of the heart and electrocardiographic abnormalities that the latter could be anticipated rather well by physical examination. When advanced electrocardiographic changes were present, the heart sounds were decreased in intensity, best described as "mushy" or dulled, prolonged as if the heart were beating in slow motion. Actually bradycardia was present as well as frequent irregular pauses.

The paralysis was flaccid as in the previous case and responded in the same dramatic fashion to sodium chloride therapy. While at times the patient was in peripheral shock, the paralysis preceded the shock and

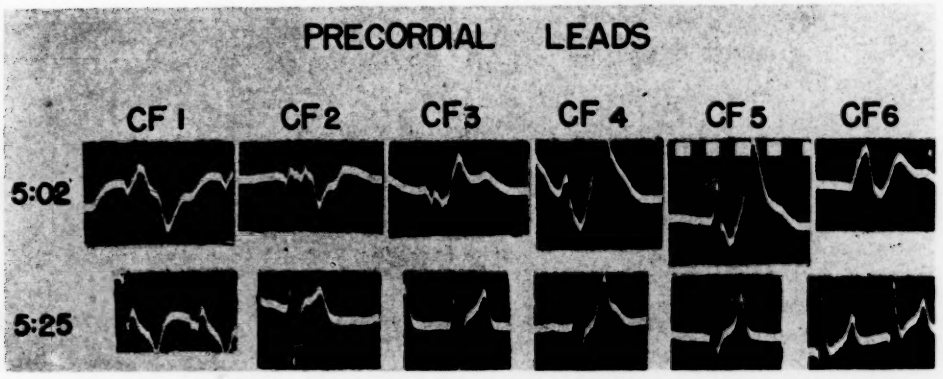

FIG. 13. *Case* II. *Multiple precordial leads corresponding to the limb leads of Figure* 12, *showing reversion of potassium effect on conduction by saline for the second time.*

could not be ascribed to it. It is worthy of note that the skeletal muscle on direct percussion was able to contract during the paralytic phase, excluding the possibility that the dysfunction was localized in the muscle itself.

GENERAL CONSIDERATIONS

Potassium Accumulation in the Body. Potassium balance is normally maintained by a dietary intake of about 3.4 Gm. per day and an excretion of an equal amount, about 80 per cent in the urine and 20 per cent in the feces.[13] Renal excretion is efficient in the presence of normal kidney function, and single doses of as large as 10 Gm. of potassium chloride are almost completely cleared in four to eight hours.[14] With severe impairment of renal function, potassium is excreted at a slower rate,[14,15] but is sufficient to maintain a normal serum potassium level in most cases of uremia.[16,17]

There are, however, a few reports of accumulation of potassium in patients with high-grade renal failure.[4,18,19] It is in this group with impaired renal clearance of potassium that the load presented to the kidney for excretion becomes important. This load will depend on both dietary intake and liberation of potassium from body tissues.

The danger of dietary potassium in the face of anuria was demonstrated by Addis and Lew,[20] who found survival time inversely proportional to potassium intake in anuric rats. Tissue trauma liberates intracellular potassium,[21] thereby increasing the renal load. Elevated potassium levels in the blood and electrocardiographic changes have been observed in the "crush syndrome."[22] Inasmuch as the red cell contains about twenty times as much potassium as the serum, massive hemolytic reactions may liberate a toxic amount of potassium. In the pig, whose red cell potassium content resembles that of man, lethal potassium levels have been obtained from blood destruction due to scalding.[23] Asphyxia increases the potassium content of serum.[24] In untreated Addison's disease there may be some elevation of potassium in extracellular tissues.[25] Hastings and Compere found potassium levels in adrenalectomized dogs as high as 20 milliequivalents/l. at the time of death,[26] reaching or exceeding lethal levels attained by infusion of potassium chloride.[27] It seems plausible that blood serum potassium may become elevated in other conditions associated with marked sodium chloride loss, i.e., salt-losing nephritis and diabetic coma. In diabetes the inability to store glucose within the cell has been shown to be associated with high serum potassium.[13] We have seen an electrocardiographic tracing with auricular standstill and T wave elevations highly suggestive of potassium intoxication in a patient with

diabetic coma which reverted to normal under therapy.[28]

Action of Potassium on the Heart. Potassium intoxication in human beings produces a typical sequence of electrocardiographic changes. A diagrammatic composite of progressive changes in limb leads based on five cases observed in this clinic and consistent with those in the literature is shown in Figure 14. These changes in order of occurrence are: (1) Elevation of the T wave; (2) decrease in size of the R wave and increase in the S component; (3) disappearance of the P wave; (4) depression of the ST segment, perhaps better expressed as obliteration of the ST segment with the T wave originating from the S wave; and (5) spread of the QRS and T waves until a smooth biphasic curve is produced.

This general sequence resembles the patterns produced experimentally in dogs,[27] cats,[29] rabbits[30] and pigs,[23] following elevation of serum potassium by a variety of means. T wave elevation was observed in the perfused heart when exposed to high concentration of potassium by McLean, Bay and Hastings.[31] It has been reported in patients receiving potassium salts by mouth[32, 33] and intravenously,[24] in untreated Addison's disease[35] and in patients with high-grade renal disease.[4, 18] Precordial leads appear to show this abnormality better than limb leads. (Figs. 6 and 8.) Advanced alterations in the electrocardiogram have been previously reported.[3, 4, 18] While there are individual variations in these tracings, they show the same spread of QRST deflections and the absence of P waves. What has been referred to as a right bundle branch block would more logically be described as a generalized impairment of conduction through the heart.

In a variety of conditions, electrocardiographic tracings may simulate those seen in potassium intoxication. The dying heart may record disorganized complexes as conduction becomes depressed over large areas of muscle. Slow nodal rhythm with auricular standstill is rare and usually due to anoxia, myocarditis or severe arteriosclerotic heart disease. The bizarre pattern of myocarditis may be misleading in isolated tracings but the impairment of conduction is focal in character, and the evolution of changes is not that seen in potassium poisoning. Organic bundle branch block may simulate the biphasic potassium curve. The presence of P waves or auricular fibrillation is helpful in diagnosis inasmuch as P waves disappear in potassium intoxication before the QRS complex spreads.

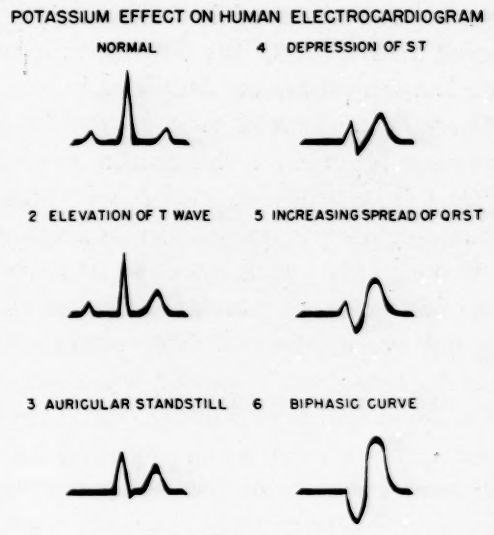

FIG. 14.

It is not possible to formulate an absolute correlation between potassium level and electrocardiographic changes in man. In human beings, however, T wave elevations were produced experimentally with elevation of serum potassium to between 7 to 9 milliequivalents/l. (27 to 35 mg. per 100 cc.).[15] P waves disappeared in our cases between 9 and 9.5 milliequivalents/l. (35 to 37 mg. per 100 cc.), and spread of the QRST complexes occurred between 9.5 and 10.5 milliequivalents/l. (37 to 41 mg. per 100 cc.).

Potassium Paralysis. Paralysis is not always present in potassium intoxication. It

has not been observed in animals dying of cardiac arrest,[27] and has not been found in some human potassium fatalities.[4]

Three proven and one probable case have been reported in this and in a previous article.[3] The onset is rapid with flaccid quadriplegia developing over a few minutes. In two cases it progressed to involve the thoracic and neck muscles but spared the first ten cranial nerves. The sensorium in all cases remained clear. Reflexes were lost in the arms and legs. Muscle contraction to direct percussion was unimpaired in one case tested. Pain sensation was intact, while two patients had some loss of vibratory sense in the lower extremities. Position sense in the feet was lost in one case. Subjective sensations were limited to numbness of hands and feet similar to paresthesias previously reported.[36]

That this is not an organic lesion of the nervous system is suggested by normal cerebrospinal fluid findings in two instances, by absence of any pathological lesion of the nervous system in the one autopsied case, and by the rapid and complete reversibility of the paralysis following electrolyte and water administration in the cases described in this report.

The paralysis is similar in its distribution to that described by Landry,[37] and the variety of conditions which may simulate potassium intoxication can be divided into three groups based on their speed of onset and reversibility:

Group A. Those developing paralysis usually over hours or days rather than minutes, showing histological evidence of nervous system damage: acute porphyria, infectious polyneuritis, ascending poliomyelitis.

Group B. Those in which paralysis may be rapid in onset and either quickly reversible or permanent, depending on length of exposure to the noxious agent: lathyrism[38] and triorthocresylphosphate intoxication.[39]

Group C. Rapidly reversible paralytic states associated with low serum potassium: familial periodic paralysis,[40] overtreated Addison's disease,[41] and chronic nephritis with low serum potassium.[42]

With knowledge of the renal status of the patient, the urinary output in the preceding week, and with an electrocardiographic tracing, no difficulty should be experienced in separating potassium intoxication from this group. In nephritis with low serum potassium, the only other condition dependent on renal damage for its evolution, the low potassium is the result of diuresis and inability of the kidney to conserve potassium. The electrocardiographic findings are the opposite of those described with potassium accumulation, presenting low T waves instead of elevation, and the neurological picture is one of weakness rather than of paralysis with areflexia.

Present observations are inadequate to explain the locus of action of high potassium on the neuro muscular unit. In Case II it was of interest that muscle contractility was unimpaired although reflexes were absent. This would place the lesion either at or proximal to the myoneural junction.

Therapy. Calcium increased the frequency of ventricular contractions. The character of the complexes was not significantly changed and there was no resumption of auricular activity. It would appear, therefore, that calcium is useful only as a temporary measure to prevent cardiac standstill by increasing ventricular muscle irritability.

Because of the observation that serum potassium is lowered when glucose is stored intracellularly, Bywaters[22] has suggested intravenous glucose and insulin to reduce serum potassium below a critical level. This would be particularly pertinent in patients with diabetic acidosis in which insulin might shift an appreciable amount of potassium into the cell.

There is evidence of pharmacological antagonism between sodium and potassium ions. Effects of lethal doses of potassium are ameliorated by concomitant sodium administration in animals.[43] In experimental shock following tissue damage in which there is a decreased amount of circulating sodium and some increase in potassium, the malignant effect of potassium and the beneficial effect of sodium chloride have been demonstrated.[44,45] In Addison's disease the sodium depletion and extreme sensitivity to potassium, as demonstrated by the Wilder test are well known.

In both cases reported in this article there was sodium depletion, in one case strikingly so. The administration of large amounts of sodium chloride rapidly reversed electrocardiographic and paralytic manifestations of potassium intoxication. This occurred in Case II with no significant alteration in the potassium level. It would appear that the potassium:sodium ratio is of considerable importance since the effect of a given level of potassium is much greater in the presence of a low sodium. It has also been demonstrated that sodium chloride alone is capable of counteracting neuromuscular block of potassium intoxication.

In addition, the first case reported shows the diuretic effect of sodium chloride in a salt-depleted patient. This functional renal impairment has been produced by sodium chloride deficiency in normal subjects,[46] and the same diuretic effect has been demonstrated.[47] It seems apparent that the sodium depletion present in our patients may have contributed to the development of both renal failure and potassium intoxication. It seems probable also that adequate sodium chloride therapy in the early phase of uremia will prevent or delay the development of potassium intoxication.

SUMMARY

Potassium intoxication in man results in widespread impairment of neuromuscular function. Potassium produces a characteristic sequence of electrocardiographic changes, impaired contraction of the heart recognizable by auscultation, and final arrest of the heart in diastole. Flaccid paralysis may also be present, involving the extremities and to a lesser degree the trunk but sparing the cranial nerves for the most part.

Two cases with elevation of serum potassium manifesting this clinical syndrome are described. Following administration of sodium chloride, both paralysis and electrocardiographic changes reverted toward normal.

The genesis of potassium intoxication, the typical sequence of electrocardiographic changes, the nature of the paralysis and the therapeutic approach are discussed.

Acknowledgment. We would like to express our appreciation to Dr. James P. O'Hare for permission to use the second case and for his helpful criticism.

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The Clinical Manifestations of Subacute Bacterial Endocarditis Caused by Streptococcus S.B.E.*

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In a preliminary publication,[1] data were presented regarding the incidence, cultural characteristics and diagnostic criteria of a previously unrecognized variety of non-hemolytic streptococcus recovered from the blood of patients with subacute bacterial endocarditis. This organism, designated Streptococcus s.b.e., was identified in sixty-two (46 per cent) of 135 blood cultures submitted from various sources for detailed study and classification. (Table I.) Streptococcus s.b.e. not only has a rather characteristic and distinctive combination of physiological properties but about 90 per cent of the strains which have been tested fall into one serological type. The few strains thus far studied which do not belong to this serological type can be grouped into one additional type.

TABLE I

STREPTOCOCCI FROM SUBACUTE BACTERIAL ENDOCARDITIS (135 CULTURES FROM VARIOUS SOURCES)

Species or Variety	No.	Per Cent	Remarks
Streptococcus s.b.e.	62	46	Apparently a new variety of streptococcus
Streptococcus mitis	44	32	The common throat streptococcus viridans
Streptococcus bovis	14	10	Similar to so-called "Bargen streptococcus"
Streptococcus faecalis	5	4	Group D; non-hemolytic enterococci
Streptococcus mastitidis	4	3	Group B; 3 hemolytic, 1 non-hemolytic
Group G streptococci	1	1	"Non-minute" variety; hemolytic
Unclassified streptococci	5	4	Not identified with any known species

The present report deals with the clinical manifestations caused by infection with Streptococcus s.b.e., with particular reference to the increased morbidity and mortality resulting from its resistance to therapy. When subacute bacterial endocarditis was a practically uniformly fatal disease it was not possible to appreciate and evaluate the unique refractoriness of this causative organism. Our group of 115 consecutive and unselected patients with subacute bacterial endocarditis treated with a combination of penicillin* and heparin[2,3,4,5] is ideally suited for this purpose because, despite the 83 per cent recovery rate (Table II), there are many patients who exhibit varying degrees of resistance to the joint treatment.

CORRELATION OF CLINICAL AND LABORATORY DATA

In order to ascertain the factors responsible for our refractory cases, including the

* We are indebted to Mr. John L. Smith of the Chas. Pfizer Co., Inc. for the unusually liberal supplies of penicillin required in the treatment of this series of patients.

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recurrences and unequivocal treatment failures, an attempt was made to establish a correlation between streptococcus typing and the clinical response. In our series of 115 patients, sixty-eight different organisms were classified and the presence of three different species established. (Table III.)

TABLE II

RESULTS WITH PENICILLIN-HEPARIN THERAPY OF SUBACUTE BACTERIAL ENDOCARDITIS (STREPTOCOCCUS VIRIDANS AND NON-HEMOLYTICUS)

		No.	Per Cent
Total No. of Cases (Consecutive and Unselected)		115	100
Duration of illness prior to therapy (weeks)	1 to 64		
Penicillin sensitivity of causative organisms (O.U.)	.007 to 2.0		
No. of Cases in Which Therapy Was Successful		96	83
Patients living	89		
Patients deceased—other causes	7		
Post-therapy period of observation (months)	2 to 28		
No. of Cases in Which Therapy Failed		19	17

Of the forty patients infected with Streptococcus s.b.e., nine were completely resistant to therapy and all nine succumbed. A tenth and eleventh patient were successfully treated and showed no clinical signs or bacteriological evidences of subacute bacterial endocarditis but succumbed to congestive heart failure subsequent to the severe valvular defect occasioned by the endocarditis. A twelfth case was a fatality due to a terminal Staphylococcus aureus infection following apparent recovery from Streptococcus s.b.e. endocarditis. The twelve fatalities following infection with Streptococcus s.b.e. included all four patients who suffered lethal intracranial hemorrhage incidental to ruptured mycotic aneurysms or cerebral embolization. Of the remaining twenty-eight patients infected with Streptococcus s.b.e. there were six recurrences, constituting all of the recurrences to date in the entire series of 115 cases.

Of the entire group of forty patients infected with Streptococcus s.b.e. only seven (seventeen per cent) responded to our standard Dosage Plan No. 1 (Table IV) with 500,000 Oxford units of penicillin intravenously and therapeutic doses of heparin over a period of five weeks. The remainder of the fifteen successfully treated patients in this group required multiple and prolonged courses of therapy with massive, intensive daily penicillin dosage before the infection could be terminated.

In contrast, twenty-two patients were infected with Streptococcus mitis, appar-

TABLE III

STREPTOCOCCUS S.B.E. AS A FACTOR IN PROGNOSIS IN A SERIES OF 115 TREATED CASES OF SUBACUTE BACTERIAL ENDOCARDITIS

Causative Organism	No. of Cases	Treatment Successful		Recurrence No.	Intracranial Hemorrhage No.	Fatal Outcome No.
		No.	Per Cent			
Streptococcus s.b.e.	40	22	55	6	4	12
Streptococcus mitis	22	19	86	0	0	3
Streptococcus bovis	6	6	83	0	0	1

Streptococcus s.b.e.: A hitherto undescribed variety of non-hemolytic streptococcus. Strains belonging to this type show distinct and homogeneous cultural and immunological reactions.

Streptococcus mitis: The common throat streptococcus viridans.

Streptococcus bovis: Similar to so-called "Bargen streptococcus."

ently more sensitive to penicillin; nineteen of these patients recovered and only three died and there were no recurrences. Six patients were infected with Streptococcus bovis; five of these recovered and only one died. Significantly, the autopsy in the fatal Streptococcus bovis infection showed healed endocarditis, death being due to intractable heart failure resulting from an inordinate loss of valve substance.[6] Twenty (71 per cent) of the twenty-eight patients comprising the combined Streptococcus mitis and bovis group recovered with the first span of treatment.

TABLE IV
TREATMENT PLANS

Plan No.	Daily Dosage Schedule		Span of Therapy, Weeks
	Penicillin Million O.U.	Heparin Mg.	
1	0.5	100–200	5
2	2.0	100–200	8
3	2.0	50	8

A comparison of the types of organisms encountered in our series with respect to *in vitro* penicillin sensitivity tests, treatment statistics and end results (Table v) is very revealing. In no instance did the probatory pretherapy penicillin sensitivity tests give any reliable index of the resistant nature of the organism. In the patient (Case 1) infected with Streptococcus s.b.e. requiring the largest total amount of penicillin (379.3 million O.U.) and the longest span of treatment in the entire series of 115 cases, the *in vitro* test indicated this organism could be inhibited by 0.25 Oxford units per cc. of test broth. This contrasts with the patient (Case 2) infected with Streptococcus mitis, with a comparable penicillin sensitivity of 0.25 Oxford units per cc. of test broth, who was successfully treated with 1 span of penicillin and heparin therapy for five weeks requiring a total of 24.3 million Oxford units of penicillin; and the patient (Case 3) infected with Streptococcus bovis, with a similar penicillin sensitivity of 0.25 Oxford units per cc. of test broth, who recovered following one five-week span of penicillin and heparin which required a total of 10.3 million Oxford units of penicillin.

TABLE V
PROGNOSTIC IMPORT OF STREPTOCOCCUS S.B.E.—COMPARATIVE TREATMENT STATISTICS

		Streptococcus s.b.e.	Streptococcus mitis and bovis
No. of cases	.....	40	28
Penicillin sensitivity—O.U./M.L			
Bacteriostasis	.....	0.008–0.5	0.008–0.25
Minimal lethal dose	.....	0.03 –2.0	0.06 –1.0
Total penicillin requirements—million O.U.	Low	2.3	0.4
	High	379.3	206.7
	Average	57.1	31.6
Treatment—days	Low	11	2
	High	205	90
	Average	64	38
Recoveries	No.	22 (55%)	25 (89%)
Recoveries with first course of penicillin and heparin therapy	No.	7 (17%)	20 (71%)
Recurrences	No.	6 (15%)	0 (0%)
Deaths	No.	12 (30%)	3 (11%)
Intracranial hemorrhage	No.	4 (10%)	0 (0%)
Total treatment failures	No.	18 (45%)	3 (11%)

CASE 1. H. S. S., age seventeen years, a female with subacute bacterial endocarditis for

FIG. 1

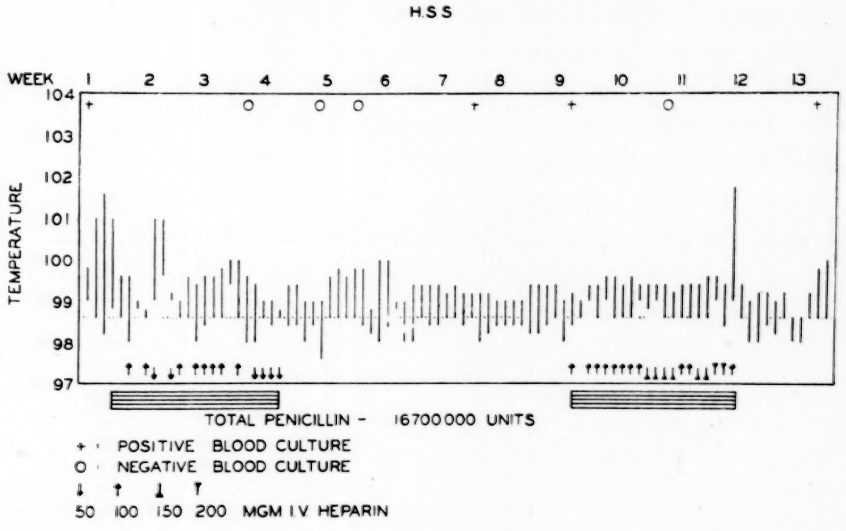

FIG. 2

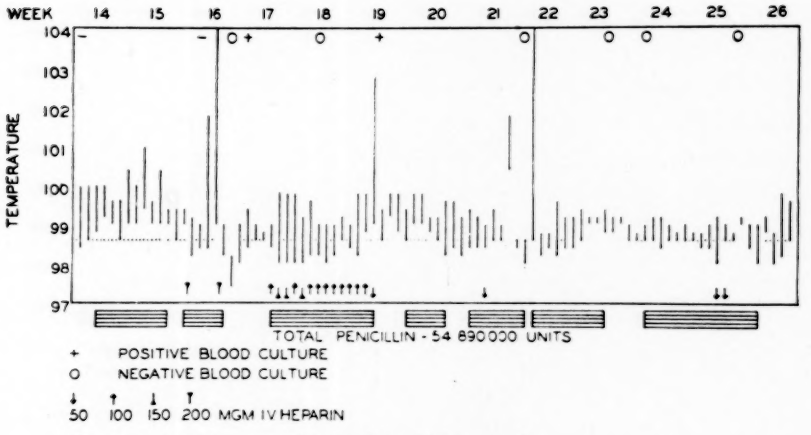

FIG. 1. *Case* I, *course during first thirteen weeks.*
FIG. 2. *Case* I, *course during fourteenth to twenty-sixth week.*

nine months, caused by Streptococcus s.b.e. (penicillin sensitivity 0.25 Oxford units); advanced coarctation of the aorta, cephalad hypertension with two episodes of intracranial hemorrhage; possible rheumatic cardiovascular disease. She showed no lasting response to intensive sulfonamide therapy at Mt. Sinai Hospital in New York and was admitted to Jewish Hospital of Brooklyn in a greatly deteriorated condition with marked weakness and emaciation (weight fifty-five pounds). During her first admission she had five courses of penicillin and heparin, comprising 205 treatment days and sixty-two weeks of hospitalization. The total penicillin administered was 142.9 million Oxford units. (Figs. 1, 2 and 3.) A recurrence took place after six months following mild follicular pharyngitis. The blood culture was again positive for Streptococcus s.b.e. The condition was retreated for fifty-six days with a daily dosage of penicillin 2 million to 5 million Oxford units for a total of 236.4 million Oxford units (Fig. 4) and minimum dosages of heparin. The over-all dosage of penicillin amounted to 379.3 million Oxford units. The patient made a dramatic response to one final span of treatment; she became afebrile, asymptomatic, with sterile blood cultures, a hemoglobin of 94 per cent and an erythrocyte sedimentation rate of 7 mm. per hour (Westergren). She now weighs 130 pounds, showing a gain of seventy-five pounds.

CASE II. D. K., age twenty-five, a female with subacute bacterial endocarditis for six weeks, caused by Streptococcus mitis (penicillin sensitivity 0.25 Oxford units); and congenital heart disease. Prior to admission to Jewish Hospital of Brooklyn she had received a total of 6 million Oxford units of penicillin without

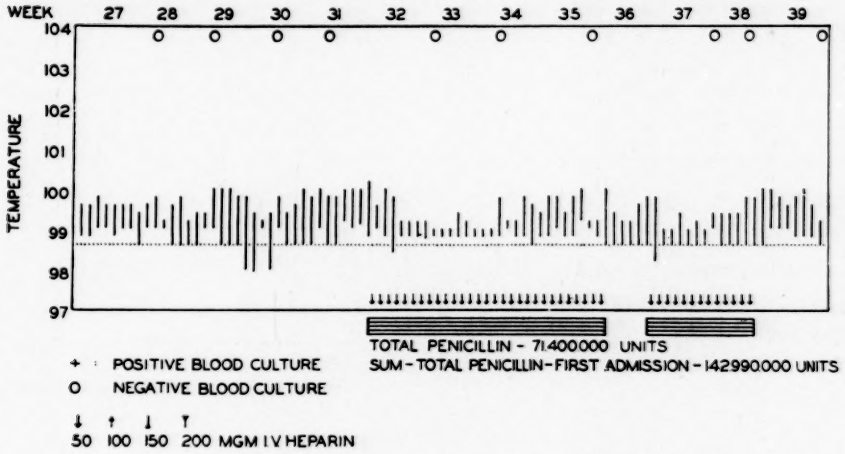
WEEK
27 28 29 30 31 32 33 34 35 36 37 38 39
TEMPERATURE
104 103 102 101 100 99 98 97
TOTAL PENICILLIN - 71400000 UNITS
SUM - TOTAL PENICILLIN - FIRST ADMISSION - 142990000 UNITS
+ POSITIVE BLOOD CULTURE
O NEGATIVE BLOOD CULTURE
50 100 150 200 MGM I.V HEPARIN

FIG. 3. *Case* I, *course during twenty-seventh to thirty-ninth week.*

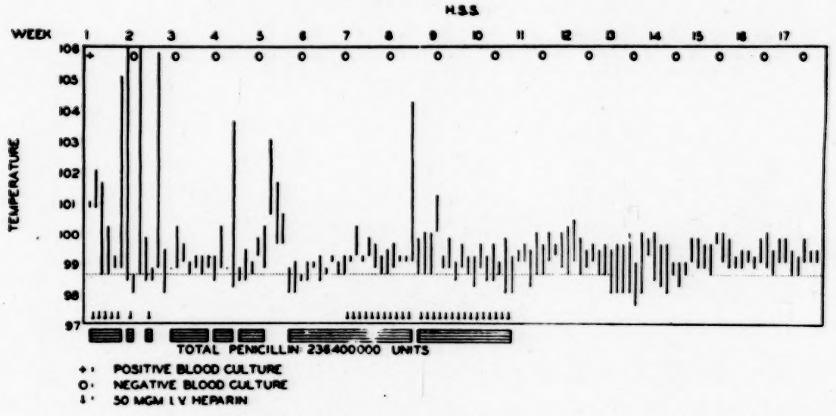
H.S.S.
WEEK
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
TEMPERATURE
108 105 104 103 102 101 100 99 98 97
TOTAL PENICILLIN 236400000 UNITS
+ POSITIVE BLOOD CULTURE
O NEGATIVE BLOOD CULTURE
50 MGM I.V HEPARIN

FIG. 4. *Case* I, *course during recurrence.*

results. She responded to one curative thirty-five day span of penicillin (22.9 million Oxford units) and heparin (2,000 mg.). (Fig. 5.) Her bloodstream was sterilized after eleven days and has remained so for thirteen months; hemoglobin is 104 per cent and erythrocyte sedimentation rate 4 mm. per hour (Westergren). Her general health is excellent and the patient has returned to gainful occupation.

CASE III. A. J., age thirty-five, a female with subacute bacterial endocarditis of five weeks' duration caused by Streptococcus bovis (penicillin sensitivity 0.25 Oxford units), together with primary rheumatic, mitral heart disease, was successfully treated with one curative thirty-four day span of penicillin (10.5 million Oxford units) and heparin (2,100 mg.). (Fig. 6.) The bloodstream was sterilized after sixteen days of therapy; blood cultures have been consistently negative for the past eighteen months; hemoglobin is 98 per cent and erythrocyte sedimentation rate 9 mm. per hour (Westergren). The patient is now in good health.

The degree, range and percentage incidence of *in vitro* penicillin inhibitability was virtually the same in all three groups of nonhemolytic streptococci compared in this review. (Table v.) It will be noted in connection with penicillin sensitivity tests, that a distinction is made between the bacteriostatic and minimal lethal dosage of penicillin, the clinical significance of which will be presented in a forthcoming report.[7]

The refractory nature of Streptococcus s.b.e. is impressively portrayed by the comparative treatment statistics. A greatly augmented daily dosage schedule of penicillin, up to 2 million Oxford units (Dosage Plan 2 or 3—Table IV), was found essential for permanent sterilization of the blood-

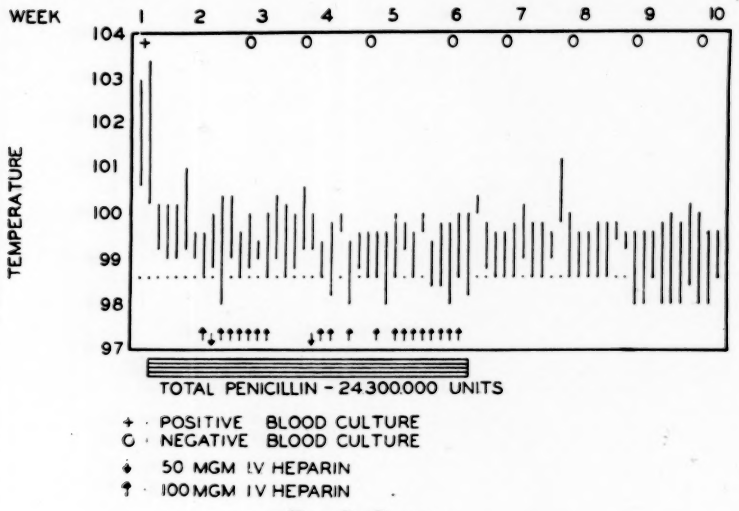

FIG. 5. *Case* II.

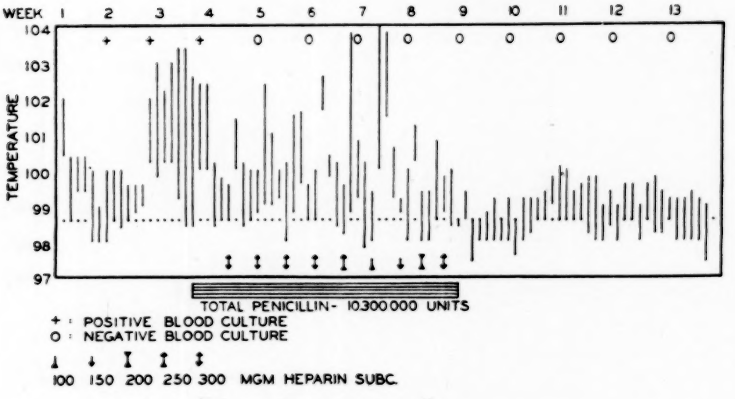

FIG. 6. *Case* III.

stream. This, together with a longer uninterrupted span of treatment, (eight weeks as contrasted with the standard five-week course) and the not infrequent necessity for re-treatment, is responsible for the marked increase in the average total penicillin requirements—57.1 million Oxford units in the Streptococcus s.b.e. group as against 31.6 million Oxford units in the combined Streptococcus mitis and bovis groups.

The greater morbidity of the patients infected with Streptococcus s.b.e. is not adequately reflected by the increased average period of hospitalization—sixty-four treatment days as against the standard thirty-five days. It has been possible through clinical observation to detect the Streptococcus s.b.e.-infected patient by the failure of the usual prompt response to standard dosage schedules and the resultant persistence of evidence of bacterial activity such as malaise, pallor, impaired appetite, continued temperature and embolic phenomena. Whenever the presence of Streptococcus s.b.e. is suspected a daily dosage schedule of 2 million Oxford units of penicillin is instituted even before laboratory confirmation is available. For reasons advanced in previous publications[8] the route of administration is by vein, if possible—our use of heparin making technically possible continuous venoclysis over the requisite prolonged treatment periods.

A review of the survival rate, morbidity, mortality statistics and incidence of recurrence (Table v) is further convincing

evidence of the prognostic import of Streptococcus s.b.e. The twenty-two recoveries (55 per cent) and twelve fatalities (30 per cent) of the Streptococcus s.b.e. series are highly significant when contrasted with the twenty-five recoveries (89 per cent) and three fatalities (11 per cent) of the combined Streptococcus mitis and bovis series. It is noteworthy that of our entire series, the four patients who succumbed to massive intracranial hemorrhage were all infected with Streptococcus s.b.e.

fore, evoked no surprise. The present status of these patients following optimum, prolonged, intensive and massive penicillin therapy is as follows: All six patients were retreated and discharged as recovered, five remaining well and one patient succumbing to a terminal Staphylococcus aureus infection. It is of interest to note that the five successfully retreated patients who have survived have continued to improve and are considerably better than after their initial treatment period.

TABLE VI

RECURRENCES. RE-TREATMENT STATISTICS

Case No.	Therapy			Organisms		Penicillin Blood Assays		Penicillin Dosage—Million O.U.			Remarks
								Daily		Total	
	No. of Courses	Days	Hosp. Days	Strep. Type	Penicillin Sensitivity O.U. Bacteriostasis	Daily Dose Million O.U.	Level O.U.	Low	High		
1. L. M.	1	44	110	SBE	0.03	1.0 2.0	1.5 3.0	1.0	2.0	85.0	Recovered
2. H. S. S.	1	56	110	SBE	0.125	5.0	5.0	2.0	5.0	236.4	Recovered
3. M. C.	3	79	140	SBE	0.125	2.0	3.0	0.5	2.0	137.5	Recovered
4. A. R.	1	55	77	SBE	0.015	2.0	3.0	1.0	2.0	144.8	Recovered
5. A. V. D.	1	50	70	SBE	0.03	0.5	0.4	0.5	2.0	55.5	Recovered
6. C. K.	1	25	70	SBE	0.25	0.5	0.3	0.5	0.5	12.5	Died; terminal Staph. aureus endocarditis.

Finally, striking evidence of the tenacity and sturdiness of Streptococcus s.b.e. is apparent from a study of the recurrences. All of the six recurrences in the entire series were due to Streptococcus s.b.e. (Table VI.) Much effort and material were expended in sterilizing the bloodstream during the initial course of treatment in five of the six cases. While the patients satisfied the criteria of a successfully treated case, with complete absence of clinical and laboratory evidence of bacterial activity for at least four weeks post-therapy at the time of the initial discharge, there were some misgivings about the permanence of the results. Recurrence of the endocarditis in these patients, there-

COMMENT

A comparison of the type of organism, *in vitro* penicillin sensitivity, dosage schedule and outcome indicates the futility of predicting the response to treatment of the patient with subacute bacterial endocarditis without knowledge of the precise identity of the offending organism. In virtually every instance the pre-therapy probatory penicillin sensitivity tests were prognostically uninformative and were practically valueless for establishing dosage schedules.

As a result of clinical experience, the failure to respond to standard dosages of penicillin has often justified the suspicion

that the patient is infected with Streptococcus s.b.e. Fortunately, because of the specific cultural characteristics of this organism and the availability of diagnostic test sera, it is now possible to obtain pretreatment laboratory confirmation of the presence of this organism.

Recognition of the presence of this new variety of non-hemolytic streptococcus may be life-saving. Whenever it is suspected, even without laboratory confirmation, it is imperative that an optimum dosage of penicillin at a level of at least 2 million Oxford units be established for a span of not less than eight weeks. Persistence with lesser dosages invites treatment failure, not only by inability to terminate the infection but also because of the tendency on the part of subcurative dosage to contribute to the resistance of the causative organism. It is comforting to know that these massive dosages of penicillin are non-toxic and are more effective in achieving the desired blood levels. Because of the superiority of the continuous intravenous drip for the maintenance of effectual serum levels of penicillin this mode of administration is recommended, the uninterrupted intravenous flow being facilitated technically by the conjoint use of heparin.[8]

The present state of our knowledge does not permit us to explain adequately why patients infected with Streptococcus s.b.e. are so refractory to treatment. Certainly the *in vitro* penicillin sensitivity tests do not throw any light in this direction. As judged by the study of necropsy material, which frequently reveals unusually destructive and undermined lesions in these subjects, it would seem that Streptococcus s.b.e. has a peculiar affinity for cardiovalvular tissues. One might also speculate as to whether penicillin-neutralizing agents are elaborated by the organism in question. It is hoped that these moot points will be clarified by experimental investigations now in progress.

SUMMARY AND CONCLUSIONS

1. A previously unrecognized variety of non-hemolytic streptococcus, designated Streptococcus s.b.e., was recovered from the blood of sixty-two (46 per cent) of 135 patients with subacute bacterial endocarditis.

2. In a consecutive, unselected series of 115 cases of subacute bacterial endocarditis due to non-hemolytic streptococci treated with a combination of penicillin and heparin, Streptococcus s.b.e. was identified as the etiological agent in forty of the sixty-eight patients in whom the infecting organism was classified.

3. A large majority of the patients infected with Streptococcus s.b.e. proved to be refractory to penicillin in standard dosage although the organism was readily inhibited by penicillin *invitro*.

4. A comparison of type of streptococcus, *in vitro* penicillin sensitivity, treatment statistics and outcome indicates the futility of predicting the clinical response without knowledge of the presence or absence of Streptococcus s.b.e.

5. Streptococcus s.b.e. was in a large measure responsible for the treatment failures and fatalities in this series of 115 cases.

6. It is noteworthy that all six recurrences in the series were due to this organism, as were all four intracranial hemorrhages.

7. The prognostic significance of Streptococcus s.b.e. and the importance of its early recognition has been discussed and an optimum treatment program proposed.

The authors desire to express their appreciation of the contributions made by Doctor G. C. White, Associate Professor C. F. Niven, Jr., Professor J. M. Sherman, and Mrs. Mary R. Washburn of the Laboratory of Bacteriology, Cornell University, Ithaca, New York. We are indebted to Miss M. Kozak for technical assistance.

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Radiophosphorus as the Treatment of Choice in Primary Polycythemia*

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"RADIOACTIVE phosphorus when obtainable is the treatment of choice at present"[1] for primary polycythemia.[2–5] Soon uranium piles will be established and then radiophosphorus will be available to all at a nominal sum.

TECHNICS, DEFINITIONS AND EQUIPMENT

Radiophosphorus (P^{32}) was obtained either from Dr. J. H. Lawrence, University of California, or Dr. Robley Evans, Massachusetts Institute of Technology. The average dose administered, as an isotonic solution of sodium phosphate containing P^{32}, to a patient at one time was about 5 millicuries.[2,5] (A millicurie is $\frac{1}{1000}$ of a curie. A curie is roughly the amount of radiation —approximately 3.7×10^{10} beta-particles given off per second by 1 Gm. of radium.) All of the administrations, which varied from 2 to 6 cc., were given intravenously. In over 2,000 administrations no nausea or "radiation sickness" has ever occurred. Additional treatment was given when relapse of the disease occurred. Remissions lasted, as a rule, from six months to as long as four years. A remission is defined as that condition in which the blood levels have returned to normal and the symptoms complained of on admission are absent. Although spontaneous remissions occur in polycythemia, I had never been fortunate enough to witness one.

Primary polycythemia appears to be an acquired disease in which there is a hyperplasia of the marrow and all of its elements. Therefore, there is an abnormal increase of the total blood volume as well as elevated red blood cell, white blood cell and platelet levels in the peripheral blood. Associated findings are splenomegaly, elevated basal metabolic rates, elevated blood uric acid levels, etc. The duration of primary polycythemia varies markedly. One author[6] stated that, regardless of therapy, patients with polycythemia do not survive more than fifteen years. Tinney et al.[7] reported eight cases of polycythemia who had the disease over fifteen years, one for twenty-three years. Rosenthal[8] has recorded cases in which patients with polycythemia survived more than fifteen years. However, it is probably true that primary polycythemia has a duration of approximately ten to fifteen years. *Secondary polycythemia* is a condition in which the peripheral red cell level is elevated usually in an attempt to overcome anoxemia. Associated findings are cyanosis, arterial blood anoxemia, etc. The duration of secondary polycythemia is determined by the process to which the polycythemia is secondary. *Familial polycythemia* is a congenital disease characterized by numerous small red blood cells but normal hemoglobin levels, normal rates of basal metabolism and normal blood uric acid levels. Familial polycythemia[9,10,11] is not incompatible with a normal human life span.

Secondary polycythemia must be ruled out because radiophosphorus quite obviously would have little or no effect upon

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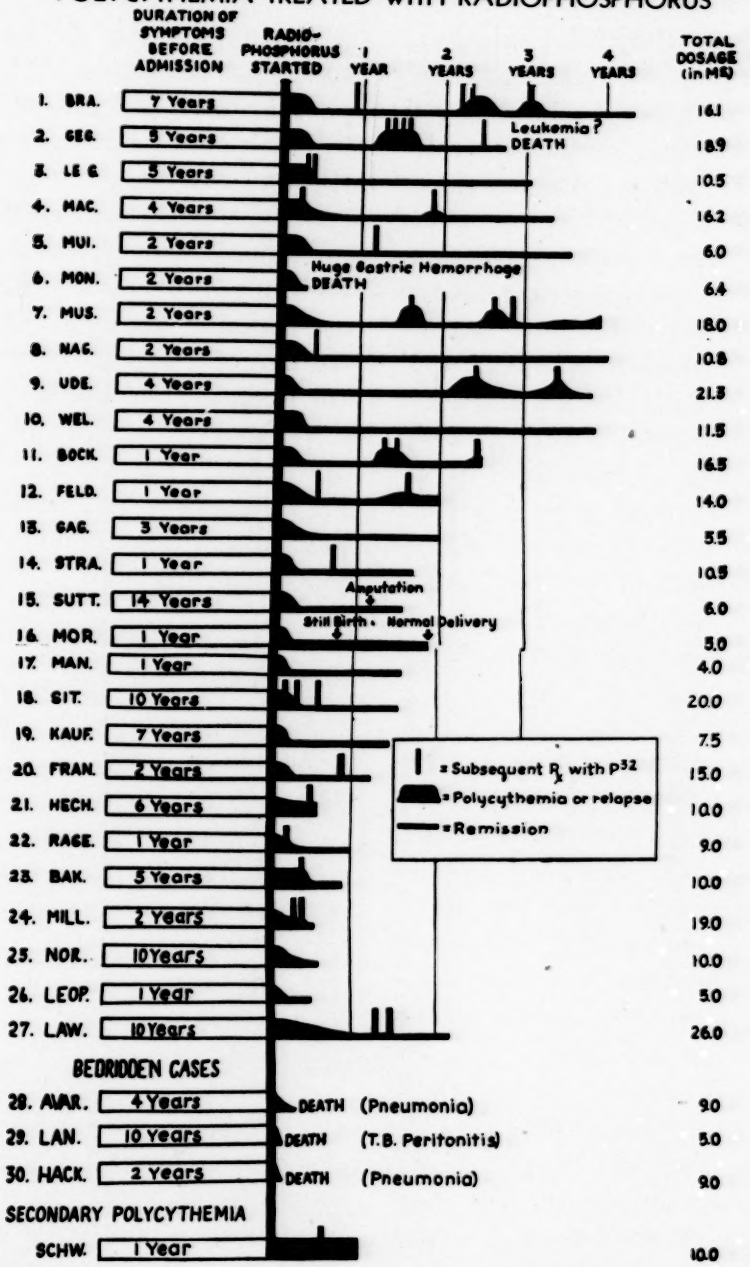
polycythemia secondary to cardiac failure, pulmonary fibrosis, pulmonary artery sclerosis, chronic carbon monoxide poisoning,[12] hypothalamic tumors, high altitudes, congenital heart disease or congenital vascular disease such as hypoplasia of the aorta. Incidentally, during the past five years we have had at least one case of each of the above mentioned types of secondary polycythemia in our laboratory. Upon all patients in this report roentgenograms of the chest were made for evaluation of the condition of the heart and lungs, roentgenograms of the abdomen to note relative size of spleen,[13] complete blood counts including hematocrit levels, in addition to complete

TABLE I

POLYCYTHEMIA TREATED WITH RADIOPHOSPHORUS


DURATION OF SYMPTOMS BEFORE ADMISSION
RADIO-PHOSPHORUS STARTED
1 YEAR
2 YEARS
3 YEARS
4 YEARS
TOTAL DOSAGE (in MC)
1. BRA. 7 Years 16.1
2. GEG. 5 Years Leukemia? DEATH 18.9
3. LE G. 5 Years 10.5
4. MAC. 4 Years 16.2
5. MUI. 2 Years 6.0
6. MON. 2 Years Huge Gastric Hemorrhage DEATH 6.4
7. MUS. 2 Years 18.0
8. NAG. 2 Years 10.8
9. UDE. 4 Years 21.3
10. WEL. 4 Years 11.5
11. BOCK. 1 Year 16.5
12. FELD. 1 Year 14.0
13. GAG. 3 Years 5.5
14. STRA. 1 Year 10.5
15. SUTT. 14 Years Amputation 6.0
16. MOR. 1 Year Still Birth • Normal Delivery 5.0
17. MAN. 1 Year 4.0
18. SIT. 10 Years 20.0
19. KAUF. 7 Years 7.5
20. FRAN. 2 Years 15.0
21. HECH. 6 Years 10.0
22. RAGE. 1 Year 9.0
23. BAK. 5 Years 10.0
24. MILL. 2 Years 19.0
25. NOR. 10 Years 10.0
26. LEOP. 1 Year 5.0
27. LAW. 10 Years 26.0
= Subsequent Rx with P32
= Polycythemia or relapse
= Remission
BEDRIDDEN CASES
28. AMAR. 4 Years DEATH (Pneumonia) 9.0
29. LAN. 10 Years DEATH (T.B. Peritonitis) 5.0
30. HACK. 2 Years DEATH (Pneumonia) 9.0
SECONDARY POLYCYTHEMIA
SCHW. 1 Year 10.0

physical examinations and carefully taken histories. The patients treated with radiophosphorus, therefore, had no significant cardiac or pulmonary abnormalities, little or no cyanosis nor evidence of arterial anoxemia but did have in most instances enlargement of the spleen, increased rates of basal metabolism, elevated blood uric acid levels, elevated white blood cell and platelet levels in addition to elevated red blood cell and hematocrit levels.

Only five of the patients in the thirty cases to be reported had not had previous treatment of some type such as *x*-radiation, phlebotomy, phenylhydrazine, etc. None had had extensive paravertebral sympathectomy[14] which increases the vascular-bed volume or area in addition to the alteration of some unknown nervous system balance and to the constriction of the caliber of the pre-sinusoidal vessels of the bone marrow.

The blood counting pipettes and chambers used were approved by the United States Bureau of Standards. Hematocrit tubes designed by Wintrobe were used.

RESULTS

The results of the administration of radiophosphorus to thirty patients with primary polycythemia and one with secondary polycythemia are shown in Table 1. Forty-one remissions were induced in the thirty primary cases; three patients had three remissions each. The duration of the remissions has varied from six months to four years and some are still continuing. No remission occurred in the patient with secondary polycythemia, although the patient received an adequate amount of P^{32}. As can be seen, the dosages for the thirty primary cases varied from 4 to 26 millicuries. In addition to the administration of radiophosphorus all of the patients were asked to refrain from eating red or glandular meats, dried fruits, beets and spinach in an attempt to reduce the daily intake of iron. Two patients, No. 21 and 24, did not cooperate in this request and their remissions occurred very slowly. In the other patients remissions occurred in sixty to ninety days. A relapse of polycythemia can be induced by giving large doses of iron. (Case No. 2.)

There were five deaths none of which could be attributed, I believe, to radiophosphorus. One patient died of myeloid leukemia, one following gastric hemorrhage (he had had gastric hemorrhages previous to the administration of P^{32}), two following pneumonia (both were bedridden as both had suffered cerebral hemorrhages with the associated paraplegia before the administration of radiophosphorus), and one of tuberculous peritonitis (this patient had developed a jejunal fistula following an abdominal operation). Postmortem examination was not permitted on the last case so it was impossible to rule out tuberculous splenitis.

COMMENT

Well over 200 patients with primary polycythemia have been treated with radiophosphorus. Below is a partial list of the cases:

	No.
Jefferson Hospital	30
University of California (Dr. J. H. Lawrence)	65
Mt. Sinai Hospital, N.Y.C. (Dr. N. Rosenthal)	40
Mayo Clinic (15)	38
Washington University, St. Louis (5)	30
University of Pennsylvania (16)	8
New England Deaconess (17)	3
	214

Ninety per cent of these patients had satisfactory remissions. Some of the failures could be attributed to insufficient amounts of radiophosphorus used, or to its use in secondary types of polycythemia and also to the refusal of some patients to maintain themselves on an iron-poor diet. At any rate, the results secured in these 200 cases are better than those obtained by any other

treatment used to date. Radiophosphorus is a "liquid type" of irradiation and is deposited directly into the bone marrow where it inhibits mitosis of normoblasts. *X*-rays must penetrate bone before reaching the marrow and therefore ten times more *x*-radiation is needed than beta-radiation (of P^{32}) in "r" units to obtain similar clinical results. A list of the deaths in this group of 200 cases follows:

	No. of Deaths
Jefferson Hospital	5
	No.
Leucopenic myeloid leukemia	1
Gastric hemorrhage	1
Tuberculous peritonitis	1
Pneumonia	2
University of California (Dr. John H. Lawrence)	5
	No.
Leucopenic myeloid leukemia	2
Hypernephroma	1
Carcinoma of the stomach	1
Carcinoma of the pancreas	1
Mt. Sinai Hospital (Dr. N. Rosenthal)	1
	No.
Hypoplastic anemia	1
Mayo Clinic	1
	No.
Leucopenic myeloid leukemia	1
Washington University	1
	No.
Leucopenic myeloid leukemia	1
	13

Forkner[18] quoted two authors who described patients suffering with myeloid leukemia who later developed polycythemia, eleven authors who described patients with polycythemia who later developed myeloid leukemia, and twelve authors in which both diseases coexisted. Tinney et al.[19] listed 163 cases of polycythemia, none of whom had radiophosphorus, but 10 per cent of whom died of leukemia. Other authors[20–22] have noted leukemia as a terminal event of polycythemia. So it is possible to state that regardless of treatment approximately 10 per cent of all cases of polycythemia will terminate in leukemia. It is because of this relationship (and others, such as, elevated rates of basal metabolism and elevated blood uric acid levels, etc., which occurs in both diseases) that many authors believe that polycythemia is but a peculiar type of chronic myeloid leukemia. This might be the explanation for the more effective inhibition of mitosis by P^{32} of the normoblasts in the marrow in cases of primary polycythemia than of the normoblasts which exist in secondary polycythemia. In other words, the normoblasts of primary polycythemia are not identical with normal normoblasts (or those stimulated to development by anoxemia). Secondary polycythemia is not associated with or terminate in leukemia.

Malignant disease can complicate any illness. We recently had a case (F. Kap. a fifty-three year old white female) who had had polycythemia vera for nine years treated only by frequent phlebotomies but who died of gastric carcinoma with metastases to the liver. Pneumonia is a well known terminal event in many bedridden cases. Because of our experience we now have decided that we will treat most cautiously bedridden patients who have primary polycythemia. Tuberculosis of the spleen as a cause of polycythemia was discussed in a previous paper.[3] Hypoplastic anemia and aplastic anemia as terminal events of polycythemia have been noted by many.[8,23] It is doubtful that any of the deaths listed above can be attributed to the radiophosphorus used.

After patients with primary polycythemia are in remission by the use of radiophosphorus they can undergo surgery without the well known complications of patients with polycythemia. Case No. 15 had an amputation of the leg without complications. One patient (Case No. 16), who had been married for years and was anxious to have children, was unable to become pregnant until two months after the initial administration of radiophosphorus. The first pregnancy was terminated as a stillbirth in the eighth month because of a

twisted cord. The second pregnancy a year later resulted in the birth of a normal girl baby.

Because of a report[24] that thyroidectomy reduced the blood levels of patients with polycythemia, six patients with primary polycythemia were given thiouracil in an attempt to prolong the remissions induced by radiophosphorus. Four of the patients developed skin rash at various periods. However, the six have had Deracil* for about a year, and their remissions may have been prolonged. It will take months before evaluation of the usefulness of this drug for polycythemia can be determined.

SUMMARY

1. Polycythemia may be primary, secondary or familial. The duration of each differs. The duration of primary polycythemia (polycythemia vera) is probably ten to fifteen years.

2. The primitive erythroid elements (normoblasts, etc.) of the marrow probably differ in each of the three entities. Radiophosphorus rather effectively inhibits mitosis of normoblasts in cases of primary polycythemia but not of secondary polycythemia.

3. Primary polycythemia may be a very chronic type of myeloid leukemia. Regardless of treatment about 10 per cent of the cases develop leukemia. Neither secondary nor familial polycythemia is known to be associated with leukemia.

4. Thirty cases of primary polycythemia that to date had forty-one satisfactory remissions following the use of radiophosphorus are reported. One patient with secondary polycythemia did not respond to radiophosphorus, as was expected.

5. If bedridden patients are treated with radiophosphorus, they should be treated most cautiously.

CONCLUSION

Radiophosphorus is the treatment of choice for primary polycythemia at present.

* Furnished by Dr. S. M. Hardy, Lederle Laboratories, Inc., New York, N. Y.

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Reciprocal Influences of Bronchial Asthma and Pregnancy*

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INCIDENCE OF BRONCHIAL ASTHMA IN PREGNANCY

THE exact incidence of bronchial asthma is difficult to determine because, as Dublin and Marks[1] have pointed out, much of the material available for analysis lacks a sound clinical foundation, and little of it reflects modern allergic concepts. Furthermore, although many statistics are available, they cannot be compared because the basis for reporting cases is not the same in every study. Diagnostic standards vary and in sickness surveys the asthmatic person not actually having an attack would be bypassed by the enumerator. Dublin and Marks also call attention to the fact that there would be no record of cases in which the condition has not been diagnosed or in which the last attack is sufficiently remote for the person to consider himself as fully recovered. Despite these limitations, reasonably trustworthy data are available. Bigelow and Lombard[2] estimated that in 1930 there were 13,000 sufferers from asthma in Massachusetts, or a ratio of 3.1 per thousand. This is only slightly less than that for diabetes mellitus and actually somewhat higher than for cancer. In a small town in Virginia, Vaughan[3] found a higher proportion—61 per thousand. Most of the other studies give a rate more nearly approximating the lower figure. The incidence of asthma increases with age, and this applies equally to women in the childbearing period[1] (Table 1 modified from Dublin and Marks). Thus, 0.4 per cent of pregnant women might be expected to have bronchial asthma if no other predisposing or protecting factors were operative.

TABLE 1
INCIDENCE OF BRONCHIAL ASTHMA ACCORDING TO AGE
(Dublin and Marks)

General Study Based on House-to-house Canvass		Groups under Continuous Observation			
Bigelow and Lombard Sample Population in Massachusetts		Sydenstricker Sample of White Families in Hagerstown, Maryland Dec., 1921–March, 1924		Collins White Families in Eighteen States	
Age Group	Incidence Rate per 1,000	Age Group	Annual Sickness Rate per 1,000	Age Group	Annual Sickness Rate per 1,000
All ages	3.9	All ages	4.1	All ages	4.2
Under 20	1.7	15–24	2.8	15–19	0.7
20–39	2.6	25–44	5.2	20–24	1.9
40–49	4.8	45–64	5.4	25–34	4.1
				35–44	3.7
				45–54	6.0

VARIABILITY OF RELATIONSHIPS BETWEEN ASTHMA AND PREGNANCY

Reports indicate that the relationship between pregnancy and asthma is extremely variable. At times the asthma improves considerably or even disappears

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TABLE II

DATA ON INTERRELATIONSHIPS OF ASTHMA AND PREGNANCY, FROM THE LITERATURE

Author	Patient	Age	Month of Onset of Asthma	Effect on Pregnancy	Effect on Child	Effect on Asthma	Sex	Remarks
Croom[4]	..	25	2nd	Spontaneous abortion 3rd month	Nonviable	Disappeared		
Masek[5]	1	34	1st	Induced abortion 4th month	Nonviable	Improved	..	Mother later eviscerated and died
	2	40	8th	Cesarean section	Viable	Improved		
Middlemiss[6]	..	..	...	Term	Viable	.....	..	Treated by hypnosis
Decio[7]	1	..	5th	Induced abortion	Nonviable	.....	..	Patient died of bronchopneumonia 5 days later
	2	..	3rd	Induced abortion	Nonviable	Asthma cured		
Bompiani[8]	..	24	6th	None	Viable	Cleared		
Schneider[9]	..	24	9th	None	Viable	Improved		
Offergeld[10]	1	35	7th	None	Viable			
	2	32	1st	None	Viable			
			1st	Spontaneous abortion 7th week	Nonviable			
			1st	Induced abortion for hyperemesis and asthma	.....	Relief		
	3	37	1st	Induced abortion	Nonviable			
	4	35	1st	Induced abortion	Nonviable			
Spiegler[11]	1	..	...	.....	.....	.....	..	Asthma disappeared during pregnancy only
	2	..	2nd	None	Viable	Improved at 6th month		
Schpoliansky[12]	..	39	1st	None	Viable	Improved	..	Asthma during pregnancy only
Ottow[13]	..	36	9th	Cesarean section	Viable	Relief	..	Subcutaneous and mediastinal emphysema
Schwarzer[14]	..	21	9th	None	Viable	Cured		
Fournier and Duplat[15]	1	..	7th	Prematurity	Nonviable			
			7th	Prematurity	Nonviable			
			None	None	Viable			
			4th	Miscarriage	Nonviable			
		36	1st	None	Viable	Relief		
Cestari[16]	..	..	1st	Induced abortion	Nonviable	Relief		
Lami[17]	..	..	...	.....	Viable	.....	F	Asthma in early month only and mild
					Viable	.....	F	Very mild
					Viable	.....	M	Extremely severe
					Viable	.....	F	Mild and early
					Viable	.....	M	Severe
					Viable	.....	F	Mild in first month
					Viable	.....	M	Severe to 6th month
		37	...	.....	Viable	.....	F	Mild first 2 months
Green[18]	1	24	8th	.....	.....	.....	..	Mother died
	2	32	...	None	Viable			
Williamson[19]	1	28	9th	.....	Viable			
	2	27	7th	.....	.....	.....	..	Mother died after morphia
	3	36	...	.....	Viable	.....	..	Free with female children (2); asthma with male children (2)

Author	Patient	Age	Month of Onset of Asthma	Effect on Pregnancy	Effect on Child	Effect on Asthma	Sex	Remarks
	4	25	...	.....	Viable	Improved during pregnancy		
	5	32	...	.....	Viable	.....	..	Free with males; asthma with females
	6	30	...	.....	Viable	Improved during pregnancy		
	7	36	...	.....	Viable	Free during pregnancy		
	8	32	...	.....	Viable	Free		
	9	32	3rd	.....	Viable	Free		
	10	41	8th	.....	Viable	.....	..	Bedfast from 8th month until delivery
			6th	.....	Viable	.....	..	Bedfast from 6th month until delivery

with pregnancy. On other occasions it is made worse. Sex of the child at times appears to have an influence on the asthma. Finally, the asthma may exert its effect upon the pregnancy.

To evaluate these problems for a proper guide to therapy, we have reviewed the reported interrelationships of asthma and pregnancy and have analyzed the effects of pregnancies in twenty-two asthmatic women observed in the Charity Hospital of Louisiana. The pertinent data in these groups are summarized in Tables II and III.

A glance at Table II will disclose the inconstancy of the relationships of asthma and pregnancy.[4–19] Asthma may improve or even disappear. One of Spiegler's[11] patients was free of asthma only during pregnancy. Williamson[19] observed less frequent attacks during the period of gestation and the puerperium. Others report the opposite observation. On becoming pregnant a previously healthy woman becomes asthmatic; or, if she had asthma before pregnancy, it becomes aggravated. We treated a patient in whom each successive pregnancy was associated with progressively more severe asthma. In her non-gravid periods the attacks would become less frequent, less severe in intensity and shorter in duration. After her eighth pregnancy—she was still under thirty years of age—sterilization was done at her request. In such cases attacks are at times of much greater severity than usual and may terminate in the death of the mother, the fetus or both. Green[18] reported a case in which both mother and child died. The patient had received considerable "sedation" of a type not specified. Inasmuch as his second patient received morphine, it may be supposed that the first did as well. In two deaths reported by Williamson,[19] morphine was used. More recently, the use of morphine, especially in status asthmaticus, has been strongly condemned. Its depressant action on the cough reflex and on the respiratory center, coupled with its bronchoconstrictor effect, have led to its displacement by more efficient drugs.

Another interesting relationship of asthma and pregnancy, noted by Williamson, is that the same mother during gestation with a male child was free from discomfort, yet had asthma when pregnant with a female child, or *vice versa*. Lami's[17] patient had severe asthma when carrying a female child, but not when carrying a male. (Table II.)

Weinstein[20] has told us of one of his patients, thirty-four years of age at the time of her fourth pregnancy, who had four children in seven years. Her first pregnancy, with a male child, was uneventful. The second sixteen months later, with a female child, was complicated by asthma during the fourth to sixth months. The third pregnancy a year later, with a male child, was uneventful. Eighteen months later, she became pregnant with a female child and had severe asthma during the third to seventh months. Several years have elapsed since her last pregnancy during which she has been free of asthma. Green has suggested that in such cases the factor responsible for the attacks comes from the developing sexual organs of the fetus. In support of this possibility are the experiments of Dorn and Sugarman[21] demonstrating a sex factor in the blood stream. By injection of male rabbits with urine from pregnant women the sex of the fetus was diagnosed eighty out of eighty-five times through changes induced in the rabbit's testicles.

The inconstant relationship between asthma and pregnancy is further seen in the time of onset of the attacks. If asthma becomes worse during pregnancy, the aggravation may appear only during the first months and be followed by improvement or complete disappearance. Again, attacks may become more severe only in the latter months of pregnancy or may start early and get progressively worse. These varied interrelationships are difficult to explain because of the complexity of factors occurring in pregnancy and exercising an influence. Williamson tried to explain the improvement seen in some women on such simple grounds as added rest and protection against constipation and excitement. Certainly such care also reduces the incidence of upper respiratory infections, a noted precipitating factor for asthma. That such simple factors play a part seems logical, but other influences must be sought to explain the aggravation of asthma in pregnancy. Some of these are detailed below.

The rôle played by the membranes of the nose and paranasal sinuses in the production of asthma, of the intrinsic type particularly, is becoming clearer. A relationship of the nasal membranes and the genitalia would seem to exist. Stromiger and Birman-Bera[22] report the case of a man who for sixteen years invariably had asthma within two days after intercourse. After cauterization of his inferior turbinates he had no further attacks. Fliess[23] has shown that during the menses the inferior turbinates are congested. Lange[24] obtained a decrease in libido by cocainization of the turbinates. Koblanck[25] showed that the premature destruction of the inferior turbinates in rabbits arrested the development of the genital apparatus and, in consequence, the females would not accept the males. Fliess has shown that there are cases of nasal obstruction during coitus with attacks of asthma and he reported other cases in which nasal obstruction disappeared during intercourse. It is well known that asthma may become worse with the menses. Amberson[26] reported four cases of women in whom comenstrual turgescence of tuberculous bronchial lesions produced periodicity of clinical effects. In a discussion of Amberson's paper Kern referred to the fact that half of normal women retain 2 to 4 kg. of water during the menses. The edema thus produced will cause symptoms if it appears at a strategically narrowed place. There exists here an obvious parallel to the hydremic plethora of pregnancy.

All of these observations indicate probable ways in which asthma may be made worse by pregnancy but there are not satisfactory data to indicate the place of any of them in the problem. Other explanations have been advanced to account for the observed reactions, all with little direct evi-

dence to substantiate them. For example, Wiechmann and Paal[27] demonstrated that in asthmatic persons there is a tendency toward alkalosis during attacks. According to Wiechmann,[28] asthma improves during the last months of pregnancy because the metabolic processes at this time tend to acidosis. Even if these observations on altered pH of the blood are accepted, and there is no evidence that they should be, cases in which attacks diminish or become less severe toward the end of pregnancy still remain to be explained.

Little assistance is to be had by scrutinizing the conditions prevailing at the menopause, for there is complete disparity of effect. At times inveterate asthma disappears at this time.[29] More frequently, asthma appears at this time. The menopause also exerts a paradoxical influence on other allergic states. Jiminez Diaz[30] believes it is likely that hyperfolliculinism is the asthmogenic factor during the menopause, although he recognizes that asthma may occur in hypofolliculinism. Maranon[31] referred to the fact that aggravation of asthma by pregnancy may appear in the fourth or fifth months, i.e., at the period of maximum intensity of the corpus luteum. It will not be forgotten that during pregnancy other endocrine alterations are produced in the adrenal cortex, thyroid and pituitary which also may act on asthma. It appears that only rarely can endocrine factors act specifically as asthmogenic agents.

Offergeld[10] interpreted asthma in his cases as essentially a vagal neurosis in the origin of which disturbances of the endocrine system play a rôle. His patients were women whose history prior to onset of pregnancy revealed some conflict or neurosis. Such altered nervous systems did not behave in a normal way when subjected to the strains of pregnancy. One can only remark that the demonstration of neurotic tendencies does not prove a causal relationship between the conflict and the disease.

Some authors blame the asthma on mechanical factors, such as diminution in the space in the thorax with consequent reduction in the vital capacity. This may play a rôle in the latter half of pregnancy but many of the most severe instances occur in the first trimester. In other cases the asthma improves at precisely the time when the mechanical impediment is greatest.

EFFECTS OF ASTHMA ON THE COURSE OF PREGNANCY

With an asthmatic mother there is an inequality of risk between the mother and child. In general, the outcome for the mother is favorable. None of the mothers in the series of cases collected at Charity Hospital died and death occurred in only four of those reported in the literature: one from bronchopneumonia, one after evisceration after cesarean section, and two after large amounts of morphine. In thirty-one pregnancies reported by fourteen European authors (Table II), pregnancy was interrupted seven times, and cesarean section was performed twice before term. There were, in addition, two spontaneous abortions, one miscarriage and two premature deliveries with non-viable offspring. Thus, of the thirty-one pregnancies, there was a fetal mortality rate of 38.7 per cent. There were an additional four cases in which interruption was seriously considered. In the Charity Hospital series of twenty-two pregnant asthmatic patients there were five spontaneous abortions with non-viable offspring in sixty pregnancies. There were three premature deliveries but the offspring was viable in one instance. In addition, there were three criminally induced abortions with non-viability and one induction of labor, because of asthma, with a living child. There is, thus, a fetal mortality of 16.6 per cent, or considerably less than the

TABLE III

DATA ON INTERRELATIONSHIPS OF ASTHMA AND PREGNANCY FROM CHARITY HOSPITAL

Patient	Race	Age	Month of onset of Asthma	Effect on Pregnancy	Effect on Child	Effect on Asthma	Sex	Past History
P. D. L.	W	25	1st	Spontaneous abortion 3rd month	Nonviable	Improved		
V D. B.	W	26	7th	None	Viable	Same		
R. D. V.	W	35	8½th	None	Viable	Improved	..	7 term births, 3 miscarriages
A. J.	C	19	1st	None	Viable	Same	F	
		20	1st	None	Viable	Same	F	
M. H.	C	32	7th	Spontaneous abortion	Nonviable	Improved	F	
		33	4th	None	Viable	Improved	F	
M. D. O.	W	24	5th	Spontaneous abortion	Nonviable	Improved		
A. S. B.	W	40	8½th	None	Viable	Improved		
E. M.	C	24	3½th	None	Viable	Same		
L. C.	C	30	4th	None	Viable	Same		
R. R.	C	27	6th	None	Viable	Improved	M	
M. B. G.	W	23	5th	None	Viable			
L. C.	W	35	6th	Aborted	Nonviable			
M. E.	C	26	8th	None	Viable	Improved	M	
L. L.	C	37	8th	None	Viable	Same		
M. S. L.	W	26	8th	Prematurity	Viable	Same	M	
		27	9th	None	Viable	Same	M	
H M. S.	W	30	1st	Prematurity	Nonviable			
		32	1st	None	Viable	Improved	F	
V A.	W	24	7th	None	Viable	.....	M	
		25	8th	None	Viable	.....	F	
M. M.	C	40	1st	None	Viable	Same		
J. T.	C	21	None	None	Viable			
		24	5th	Aborted	Nonviable	Improved		
		26	4th	None	Viable	Improved		
		27	1st	None	Viable	Improved		
		31	1st	None	Viable	Improved		
		35	1st	Prematurity	Nonviable	Improved		
S. G.	C	15	1st	None	Viable	Improved	F	
		16	None	Criminal abortion	Nonviable			
		17	None	Criminal abortion	Nonviable			
		18	6th	None	Viable	Improved	M	
		20	None	None	Viable	.....	M	
		22	None	None	Viable	.....	F	
		25	None	None	Viable	.....	F	
		27	1st	None	Viable	.....	M	
		28	1st	None	Viable	.....	M	
		30	1st	None	Viable	.....	M	
		32	None	None	Viable	.....	M	
		34	7th	None	Viable	.....	F	
		35	None	Criminal abortion	Nonviable			
S. R.*	C	17	None	None	Viable	.....	M	
J. S.†	W	29	Varied	None	Viable			

* This woman had 10 pregnancies. The first asthma appeared with the third pregnancy. Asthma became progressively worse with each pregnancy. It was necessary to induce labor in the last pregnancy because of the severity of the asthma.

† Each succeeding pregnancy was associated with progressively more severe asthma. After her eighth pregnancy sterilization was performed at the patient's request.

European experience. If the criminally induced abortions are excluded, the fetal mortality drops to 11.1 per cent. If the Charity Hospital practice (Table III) represents a fair sample of obstetrical thought, it would appear that Americans are considerably more conservative, for there was but one induction of labor because of asthma in this hospital (1.66 per cent). By contrast, the European incidence of interruptions of labor was 22.6 per cent (seven of thirty-one). Though interruption of pregnancy is indicated rarely, every effort should be made to tide these patients over until such time as viable offspring may be anticipated. If delivery occurs at a time when extra-uterine life is possible, labor proceeds normally and the cough and dyspnea disappear. There is always the possibility of premature rupture of the membranes with increased fetal and maternal complications. If the child is born alive, it develops normally. There are no contrary reports in the literature. In spite of severe dyspnea, however, premature contractions seldom occur. All authors are in agreement that emptying of the uterus is followed by improvement. It would be better to say that a *status quo ante* could be reached than that the condition will be cured, for the prepregnant state may be duplicated. At least, the severe dyspnea is relieved and even though the cough persists for a time, its character changes and the expectoration decreases. The cases observed by Offergeld were dramatic in that the dyspnea disappeared immediately on awakening from the anesthetic. In the entire literature reviewed, as well as in the Charity Hospital series, there were no instances in which the patient became worse after delivery. Offergeld argues, however, that interruption of pregnancy should be considered more often. In his experience, and indeed in the European literature, a relatively high percentage of fetuses are lost, especially in the early months. Although he believes that waiting too long may be dangerous, he does point out that in the second half of pregnancy there is a tendency for the attacks to become less intense. Intrauterine fetal death becomes less frequent as fetal age increases, hence one should defer inducing labor as long as possible.

In a follow-up of his cases, Williamson brought out some arresting data as to the prognosis in the child. Fifty-eight per cent of the children in whom the mother had pre-existing asthmatic attacks showed some form of allergic reaction before the age of ten years. In those instances in which the father also exhibited some type of sensitivity this figure rose to 72 per cent.

EFFECTS OF SPECIFIC DESENSITIZATION ON THE COURSE OF PREGNANCY

Any physician who treats allergic diseases specifically will encounter reactions which convey information regarding the specificity of diagnosis and the dosage and frequency of subsequent injections. It is a rare patient who does not experience a local reaction during the course of desensitization but these are of considerably more moment to the patient than to the physician. However, generalized reactions ranging from malaise to death sometimes occur. The more severe reactions duplicate one or more of the allergic syndromes. The shock organ which responds will determine what symptoms are present clinically. Thus, if the bronchiole responds, respiratory distress will supervene. Cooke,[32] in 1922, reported an untimely and scanty menstrual flow following acute cramp-like pains in the lower abdomen, the result of pollen injections. He had two such cases and in both the symptom was part of an immediate reaction with asthma, coryza and urticaria, the menstrual flow itself not being apparent until three hours later and lasting only one day. He adds that "among many pregnant women tested and treated no such symptom has ever appeared, but extreme caution is always taken in such cases for abortion might be induced." In

1928, Kahn[33] reported a case of a woman in the first month of pregnancy who complained of excruciating pain in the lower abdomen twenty minutes after receiving an injection of grass pollen. The patient, a multipara, described the pain as similar to labor pains but more steady. There was no bleeding and the pain subsided by the following day. The following year Robinson[34] described a patient with uterine pain as a part of a constitutional reaction in which there was no bleeding. Such cases may end in abortion.[35] In a discussion of Francis' paper, Vander Veer remarked that although he had seen possibly not more than one or two miscarriages following a constitutional reaction, he had observed a number of cases in which women had abdominal and uterine cramps which would have led to abortion had pregnancy existed. Osgood also discussed the case of a pregnant woman treated successfully with epinephrine. At the same time, Huber reported an abortion after a mild constitutional reaction.

In a continuing series of letters[36] to the International Correspondence Club of Allergy (Table IV) there was a total of 202 pregnant women treated with allergen injections. Of this group, eleven suffered constitutional reactions but none aborted. On the other hand, one of the women aborted at a time when it was clear that the injection had nothing to do with it. Ratner[36] has expressed the opinion that it is theoretically inconceivable for a pregnant uterus to respond to so potentially weak a reaction as the allergic one. His view was based on certain facts, among them that in the Schultz-Dale experiment a sensitized uterine strip must be virgin in order to contract when it comes in contact with the specific antigen. Again, when a strip is taken from an animal in estrus or during pregnancy the normal resistance of such a muscle is entirely too great to be affected by the allergic reaction. Ratner concluded that the expulsion of the fetus by women who had experienced severe generalized reactions could be caused by heroic treatment. The effect of epinephrine on the human uterus remains controversial but the weight of evidence favors the statement of Brown and Wilder[37] that "the human uterus responds . . . to epinephrine quite consistently by contraction." Francis' patient was not treated with epinephrine and from the experience of Cooke and others it is clear that the human uterus, pregnant or not, can respond to antigen overload. In spite of this, there is no reason why the mother should not be treated as though she were not pregnant provided due care is taken, particularly with regard to the type and amount of sedation. The danger of interrupting pregnancy is extremely slight and far less than that caused by untreated asthma.

TABLE IV
EFFECTS OF SPECIFIC DESENSITIZATION ON COURSE OF PREGNANCY

Author[36]	Number of Pregnant Women Treated	Number of Systemic Reactions	Number of Abortions from Systemic Reactions	Number of Abortions without Systemic Reactions
A. H. Braden	15	0	0	0
G. C. Grout	32	2	0	0
Michael Zeller	12	1	0	0
M. T. Davidson	"Many"	0	0	1
J. P. Henry	63	0	0	0
W. L. Beecher	12	0	0	0
Ralph Bowen	12	0	0	0
B. A. Menace	4	0	0	0
V. J. Derbes	37	8	0	0
S. R. Zoss	17	0	0	0
Summary	202	11	0	1

SUMMARY AND CONCLUSIONS

As a guide to rational therapy we have analyzed the varied interrelationships of bronchial asthma and pregnancy. The liter-

ature has been reviewed and a series of patients has been studied. The following conclusions have been reached:

1. At times bronchial asthma improves considerably or even disappears with pregnancy. On other occasions it is made worse.

2. Sex of the child at times appears to have an influence on the asthma.

3. The asthma may exert its influence on the pregnancy and tends to increase fetal mortality.

4. Emptying of the uterus consistently improves bronchial asthma, or at least duplicates the pre-pregnant condition. Interference with pregnancy, however, is rarely indicated.

5. Though reactions may follow specific desensitization in the treatment of pregnant women, it is believed that the danger of interrupting pregnancy is extremely slight and far less than that caused by untreated bronchial asthma.

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Reviews

The Diagnosis and Management of Rheumatic Fever*

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RHEUMATIC fever is essentially a chronic disease in the same sense as tuberculosis and syphilis. In spite of incomplete reporting of cases, the death rates for rheumatic heart disease and acute rheumatic fever are high. According to Armstrong and Wheatley,[1] in the ages five to nineteen, it is the leading cause of death. (Fig. 1.) Mortality rates do not tell the whole story, as this infection is responsible for a large fraction of cardiac deaths and for heart disease which hampers the efforts of thousands in the most productive years of life. Clues to the size of this group[2] are obtained by medical surveys of school children (0.3 to 4 per cent and higher) and in the medical examination of draftees. It has been estimated that up to July, 1943, approximately 100,000 men were rejected for military service because of rheumatic heart disease.[3] Special studies on some of these cases were accomplished.[4]

Epidemiological studies show a correlation between rheumatic fever and such socio-economic factors as crowded, urban, unhygienic living conditions and poor nutrition. These non-specific factors are associated with many diseases. The last—poor nutrition—can be largely discounted; it certainly was not a significant factor in the disease as seen in the armed forces. Rheumatic fever does occur among the wealthy and upper middle classes. At present the distinction between urban and rural areas is less significant due to transportation and central schools. Dampness can be eliminated as a necessary factor since the disease is common in the Rocky Mountain area which is extremely dry.[5] Good evidence has been adduced that rheumatic fever is a familial disease.[6]

The most important of the inducing factors is the rôle of Group A beta hemolytic streptococcus.[7] Rheumatic fever is only one of the diseases that may follow such streptococcic infections. It is a non-suppurative complication, as is acute diffuse glomerulonephritis.[8] The manner in which hemolytic streptococcus actually induces these diseases is still a mystery.

Whenever an epidemic of rheumatic fever occurs in a school, a military camp or a hospital it always follows an epidemic of streptococcal infection.[2] Fortunately, the reverse is not always true; that is, not all epidemics of hemolytic streptococcal disease, such as follicular tonsillitis, septic sore throat or scarlet fever, are followed by rheumatic fever. Nor is it correct to state that the severity of the streptococcal infection has any relation to the development of rheumatic fever. It has none. Approximately 25 per cent of soldiers in the Army Air Forces who developed rheumatic fever denied any respiratory illness preceding the onset of the disease.[9] I believe that these soldiers had had a mild attack of hemolytic streptococcal disease. This is based on the

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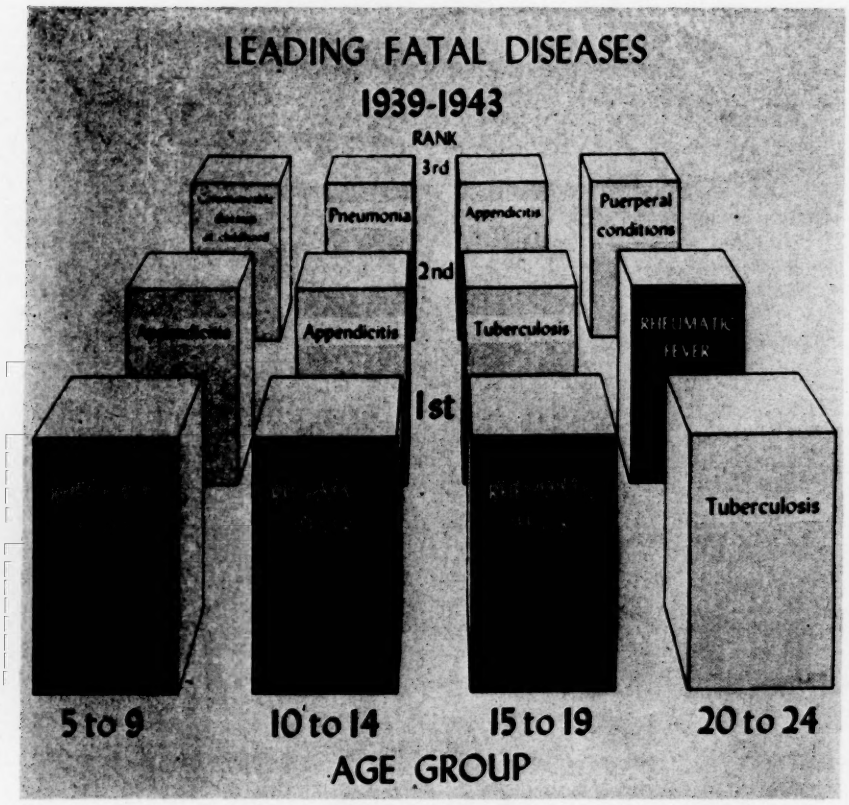

FIG. 1. *Leading fatal diseases in four age groups. Prepared by Welfare Division, Metropolitan Life Insurance Co.*

following three observations by many investigators:[10] (1) Where upper respiratory infections were studied bacteriologically, rheumatic fever occurred only in those who had hemolytic streptococcus infection, not in those with a virus infection or an infection caused by other micro-organisms. (2) In closed colonies, as the Irvington House, where routine throat cultures are done at weekly intervals, it has been shown by Kuttner that recurrent attacks of rheumatic fever occurred only in those children who acquired a new type of hemolytic streptococcus in their throat. (3) The majority, even those with a negative history of respiratory infection, showed immunologic evidence of recent streptococcal infection, when antistreptolysin titer determinations were made.

Once a streptococcic infection develops it is too late to prevent rheumatic fever. This does not imply that rheumatic fever follows every streptococcal infection, even in persons known to be susceptible. Definite figures are not available but it is estimated that 25 to 50 per cent of those who have had rheumatic fever, the known susceptibles, are likely to develop a recurrence if they acquire a streptococcic infection.[11] The initial attack rate is considerably lower. It is estimated to be from a fraction of 1 per cent to 15 per cent.

I stress these points because of the confusion between the results of the use of sulfonamides prophylactically, to prevent streptococcal respiratory infection, and the use of the same drugs therapeutically in certain bacterial respiratory diseases. If prophylactic sulfonamides serve their purpose, they prevent recurrences of rheumatic fever. Their use is limited, however, by the existence of sulfonamide-resistant strains of streptococci, as well as their potential toxic effects.

TABLE I

APPROXIMATE COMPARATIVE INCIDENCE OF VARIOUS RHEUMATIC MANIFESTATIONS IN DIFFERENT AGE GROUPS

Manifestation	Infancy	Childhood	Early Adult Life	Middle Age	Old Age
Carditis	++	++++	++	+	+
Subcutaneous Nodules	±	++	+*	−*	−
Chorea	+	+++	±**	−	−
Erythema Marginatum	+	+++	++	+	−
Typical Polyarthritis	±	+++	++++	++	+
Atypical Persistent Arthritis	−	±	+	++	+
"Growing Pains"	±	++++	++	−	−
Other Vague Symptoms	+	++++	++	+	−

* Patients in this age group with rheumatoid arthritis have similar nodules.
** Chorea of pregnancy occurs in this group.

There are certain peculiarities about rheumatic fever. It is considered a disease of childhood because this is the period of greatest vulnerability to first attacks. Although first attacks of rheumatic fever occur most frequently between five and ten years of age, and although susceptibility to initial and recurrent attacks declines rapidly in the years after puberty, rheumatic fever is common during adolescence and young adult life, as experience in the War has nidicated. Medical problems concerned with both active and inactive rheumatic fever are common in the third and fourth decades of life, especially problems in connection with heart disease.

The manifestations of the disease and the ease of recognition vary with the age of the patient. The diagnosis is easier in older children and young adults because one is more apt to see the typical polyarthritis syndrome. Table I,* which is taken from Swift and McEwen,[10b] lists the varying signs and symptoms in relation to the age of the subject.

* Reproduced by courtesy of Oxford University Press, New York, N. Y., publishers of Oxford Loose-Leaf Medicine, and the authors.

Another fact, scarcely mentioned in the literature, is that the clinical manifestations vary with the climate. Rheumatic fever can and does occur in *any* climate if Group A hemolytic streptococci are present. In general, hemolytic streptococcal infections are less frequent in tropical and subtropical climates. These organisms, however, are brought to such climates with the transfer of troops in war time and with the arrival of travelers and vacationists from northern areas, especially during the winter months. From the southern sections of this country recent reports[12] indicate that rheumatic heart disease is *not* uncommon. In fact, these studies indicate that it is frequent; so obviously rheumatic fever must occur and occur frequently. The point is that the typical, easily recognized forms of the disease do not occur in warm climates. An important corollary to this observation is the folly of sending patients with a recent attack of rheumatic fever to southern resort areas. In convalescent care a major factor is the avoidance of streptococcal infections, so if patients are sent south they should go to the places "off the beaten path" and

assiduously avoid crowds and attendant exposure to infection. Aside from the fact that it is more pleasant in sunny warm regions, they can convalesce equally well, in most instances, near their homes.[13] Climate has been discredited as of importance in the management of tuberculosis and I believe it can be discarded in rheumatic fever.

DIAGNOSTIC FEATURES

Rheumatic fever is often confused with other infectious or arthritic diseases. Fever, fatigability, loss of or failure to gain weight should suggest, especially in a child with a positive previous or family history of the disease, the possibility of rheumatic fever. But other subacute or chronic infections, blood dyscrasias or metabolic dysfunctions can produce such symptoms. In rheumatic fever, as in other febrile illnesses, there is often a leukocytosis, an increased erythrocyte sedimentation rate and a secondary microcytic anemia. In all fevers of unknown etiology, the heart should be carefully examined, not only during the *acute* stage but for several weeks thereafter.

This point I cannot emphasize too much for several reasons. First, and in a positive way, the presence of carditis frequently clinches the diagnosis of rheumatic fever. Second, and in a negative sort of way, the presence of a soft blowing systolic murmur during any acute infection is common, especially in the presence of tachycardia. Such a murmur is all too frequently interpreted as an indication of permanent heart disease. If subsequent examinations were accomplished after the infection has subsided and the pulse rate is normal, such tragic misdiagnoses would be few by virtue of the fact that the murmur had disappeared.

CARDITIS

When the physician suspects rheumatic fever he should search for manifestations of infection of any part of the heart. Carditis should always be suspected when the pulse rate is not in accord with the temperature, or when it is excessively labile. It may be considered present, according to Jones,[14] if any of these five features develop: (1) Cardiac enlargement, (2) a significant murmur, (3) pericarditis, (4) congestive heart failure, and (5) certain electrocardiographic changes.

Cardiac enlargement needs no comment. It indicates heart disease. In equivocal cases a teleroentgenogram or a fluoroscopic examination should be obtained.

There will always be quibbling as to what murmurs are significant in the course of acute rheumatic infection but in general a loud, long, apical systolic murmur, heard over a wide area and independent of position and respiration may be considered significant, as well as any *diastolic* murmur. Soft or faint systolic murmurs by themselves cannot be accepted as unequivocal evidence of cardiac inflammation. The commonest of the so-called "functional"—better termed physiological or accidental—murmurs is the loud systolic murmur heard best at the pulmonic area while the patient is recumbent and the breath is held after a forced expiration. Many murmurs heard during the acute phase of rheumatic fever disappear. There may or may not ensue scarring and deformity of the valves—the manifestations of chronic rheumatic valvular disease.[15]

Pericarditis is manifested by a friction rub with or without a detectable effusion. It is to be suspected if the patient complains of substernal or precordial pain. A leathery to-and-fro friction rub synchronous with the heart beat is diagnostic proof. Later, as fluid collects in the pericardial sac, the rub seems to move toward the base, the heart sounds become fainter and the area of cardiac dullness is increased. There may develop signs of pulmonary consolidation

at the angle of the left scapula, or more rarely cardiac tamponade.

Congestive heart failure requires little explanation except to emphasize that right-sided failure may dominate the picture; so a search for an enlarged liver and evidences of increased venous pressure is indicated.[16]

The electrocardiogram is of aid in the diagnosis of carditis. A prolonged P-R interval (0.21 sec. or more) will be encountered most commonly. It indicates that that auriculoventricular conduction time has been impaired and, if other evidence of rheumatic fever is found, the presence of carditis is affirmed. The age of the patient and the heart rate should receive consideration and the diagnosis of rheumatic fever should never rest solely on a prolonged P-R interval. Fluctuations of more than 0.04 sec., allowing for changes in heart rate, are more important than a single tracing with a prolonged interval. A recent report by Robinson[17] exposes the treachery of the atropine test as a diagnostic aid. From his observations it appears clear that atropine cannot be used to differentiate between the prolongation of the P-R interval caused by vagotonia on the one hand and rheuamtic fever on the other, for the P-R interval is shortened by atropine in both these conditions. These experiments present additional evidence that impairment of conduction in acute rheumatic fever is due, in part at least, to an increase in vagal tone, as Bruenn[18] originally suggested.

Other electrocardiographic changes will be found from time to time, such as S-T segment abnormalities, inverted T waves, and transient changes in the electrical axis during heart failure. These changes also are not of themselves indicative of carditis. They are, however, highly suggestive in the presence of other manifestations.

Recent articles by Graybiel[19] and others[20] have tended to confirm the suspicions of many that the range of the normal electrocardiogram is wider than was supposed in the past. Great caution is indicated in attaching significance to minor deviations from the normal. Diagnosis should not be based on the electrocardiogram alone.

Once the presence of rheumatic fever has been determined, the potentiality of heart disease is ever present until the active infection has subsided. Even then morphologic cardiac changes *may* have occurred, demonstrable only at a later date[21] or by more accurate observation. Estimates, correlated with the diligence of the search, range from 50 to 95 per cent of rheumatic fever patients having some cardiac involvement during the acute stage. Many must go on to complete healing from a clinical view point. Microscopic lesions may persist but they are of no practical or clinical importance.

OTHER MAJOR MANIFESTATIONS

The joint involvement in rheumatic fever typically is a migratory polyarthritis involving the large joints such as the knees, ankles, wrists, elbows or shoulders. The individual joint becomes red, hot and swollen, with exquisite pain on motion. It is well known that this type of arthritis is uncommon in children. It is also uncommon in any age group in hot climates.

It needs to be emphasized that painful joints which appear normal to the examining eye and hand may be just as important indicators of the presence of active rheumatic fever as red, hot and swollen joints. The presence of arthralgia should stimulate frequent search for evidence of carditis or other manifestations of rheumatic fever. Arthralgia alone, without other signs of active infection or previous history of rheumatic fever, should rarely be accepted as positive proof. It is admittedly difficult to evaluate the "growing pains" of childhood and only repeated observation may clarify the diagnosis. During this period constant

search for other signs of rheumatic fever or other infections, postural or orthopedic defects must be maintained.

Chorea is seen most frequently in the prepuberty period. The clinical picture of involuntary and uncoordinated movements is usually easy to bring out during the examination by requiring the child to walk or write, pick up objects or button his clothes. Early cases may show only emotional instability unless some tests of muscular coordination are employed.

A characteristic lesion of rheumatic fever is the subcutaneous nodule. These tend to appear in crops around joints and on bony prominences. They are usually seen in the severest cases. Erythematous skin lesions, particularly erythema marginatum, are significant. Purpuric rashes may also occur, but the relationship of Schönlein's and Henoch's purpura to rheumatic fever is still obscure.

It is always important to determine whether the present attack of rheumatic fever is the first one. Since the disease is characterized by recurrences, a past history lends helpful weight to the diagnosis in a doubtful case. A positive history also increases the possibility of detectable heart involvement. There may be evidence of acute rheumatic heart disease, of old cardiac involvement alone, or signs of old and recent involvement.

The history of a recent hemolytic streptococcus infection, especially if followed by a period of apparent good health for one to three weeks, is of value and a point in favor of rheumatic fever.

The response to salicylates is seldom a decisive diagnostic aid. Salicylates should be withheld while the patient's complaints are being evaluated. The fact that many painful conditions of the musculoskeletal system, other than rheumatic fever, respond strikingly to salicylates is a pitfall that must be borne in mind, as well as their non-specific antipyretic effect. Unfortunately, the response to salicylates is most dramatic when the diagnosis is least in doubt. It is of least help when the need for help is greatest, i.e., when vague symptoms and equivocal signs are the predominant clinical findings.

MINOR MANIFESTATIONS

There are other signs and symptoms designated as minor manifestations by Jones.[14] Among these are abdominal pain, often in the right lower quadrant. In the absence of other findings of rheumatic fever the differentiation from acute appendicitis is almost impossible. It takes a courageous clinician to recommend further observation rather than operation under such circumstances. On the other hand, if other stigmas of rheumatic fever are present, observation rather than immediate laparotomy is usually indicated.

Precordial pain, usually transient, is encountered during the acute stage even in the absence of pericarditis. This symptom, when it develops in the convalescent phase, is frequently an indication of cardiac neurosis.

Unexplained epistaxis should lead to a search for other signs of the disease. Pulmonary findings are rarely of diagnostic aid, although lesions in the lungs and pleurae can and do occur. Frequently there is recurrence of a sore throat at the onset of rheumatic fever. This rheumatic pharyngitis or tonsillitis is indistinguishable from non-rheumatic throat infections. It should be differentiated from the inducing hemolytic streptococcal infection. Considerations of the various chronological phases in the development of the rheumatic state will aid.[22]

As I have indicated and stressed, the diagnosis of rheumatic fever depends on evaluation of all the clinical data. No

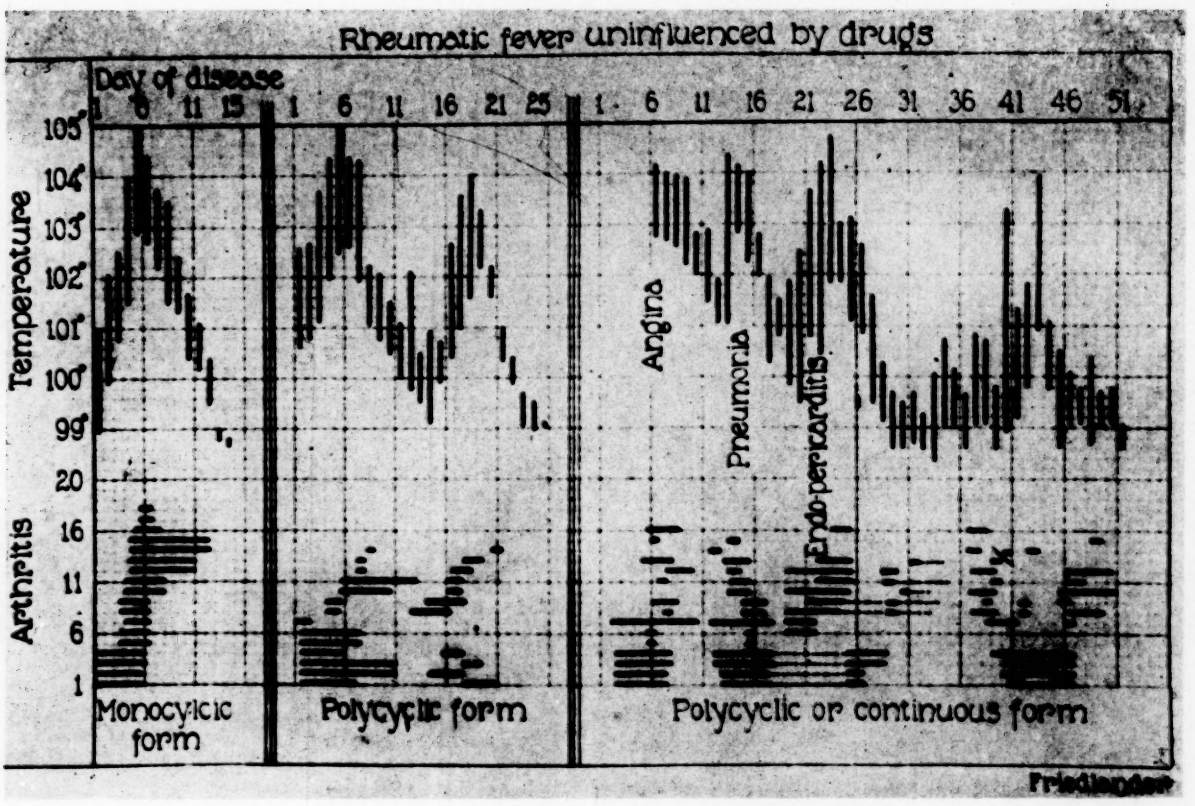

FIG. 2. *Forms of rheumatic fever. Prepared by Dr. Homer F. Swift from an article by Friedlander in Verhandl. d. Cong. Inn. Med.*, 5: 381, 1886.

laboratory test is specific; the diagnosis must be made by a physician and not by a technician. The test used most often as an aid in diagnosis, and in following the course of the active infection, is the sedimentation rate of the red blood cells. This test is not infallible; in congestive heart failure it is sometimes normal, in chorea it may be normal and most important of all, and perhaps least appreciated, is the fact that it is decreased by large doses of salicylates.[23]

Figure 2* illustrates the various clinical courses of the disease. The monocyclic form may be of short duration so that the diagnosis may easily be overlooked in such cases, or misdiagnosed as an arthralgia associated with an upper respiratory infection when in reality one is dealing with true rheumatic fever and the inflammation in the respiratory passages is merely another of the protean manifestations of this disease.

* Reproduced by courtesy of Dr. Homer F. Swift, Rockefeller Institute for Medical Research, New York, N. Y.

EVALUATION OF MURMURS

Before considering the management of the patient with rheumatic fever a few words about the diagnosis of heart disease, with particular reference to the interpretation of murmurs, are in order. The practicing physician is perforce concerned with problems of treatment and management rather than diagnosis alone. I am not overlooking the fact that intelligent handling is dependent upon accurate diagnosis. In the case of murmurs of the heart, it is obvious that treatment is not always advisable or even needed.

Any diastolic murmur means heart disease. Treatment, however, is not available for mitral stenosis or aortic insufficiency, which such a murmur connotes. Treatment

is required only for heart failure or active cardiac infection. And I hasten to add that young persons with uncomplicated rheumatic valvular heart disease develop heart failure only when active infection of the myocardium is present. Mechanical failure as the result of valvular damage alone is exceedingly rare.

Systolic murmurs may be accidental or may be due to organic disease. When organic heart disease exists, other signs or symptoms will often be present. The most common physical finding will be evidence of enlargement of the heart or a diastolic murmur. It is a serious mistake to think only of organic mitral insufficiency on hearing a systolic murmur at the apex. Except in children and in those with a recent rheumatic infection, mitral insufficiency is rarely found without mitral stenosis.

It is not my purpose to discuss the physical diagnosis of heart disease. But a search for other evidences of heart disease, particularly those indicating myocardial insufficiency or myocarditis, is important whenever a systolic murmur is heard. This is a matter of establishing a complete cardiac diagnosis.[24] If no disease or no congenital anomaly is established, no restriction of activity because of a systolic murmur is essential or desirable. Intelligent observation and re-examination at intervals with special attention to the function (efficiency), the size and the presence or absence of infection of the heart suffice. Attention must also be given to any changes in the characteristics of the previously discovered systolic murmur, or the appearance of new murmurs, especially if the latter are diastolic in time. Such findings indicate the diagnosis and to some extent the prognosis[25] but changes in the management of the patient are indicated only if signs of heart failure or active rheumatic infection are discovered.

MANAGEMENT AND TREATMENT

The sole purpose of treatment is to return the individual to normal life as soon as possible. Once active infection subsides convalescence can proceed rapidly, but it is difficult to determine when active infection has subsided. The erythrocyte sedimentation rate and the pulse rate are valuable guides but again the decision must be made by critical evaluation of all the clinical and laboratory findings.

A frequent and a major problem observed during the handling of patients with rheumatic fever is the development of anxiety states with reference to the heart. During recent years much attention has been given to the problems of convalescence and rehabilitation in injuries and chronic diseases.[26] There was and perhaps still is a tendency on the part of some to eliminate bed rest entirely. This swing of the pendulum, just as the swing in regard to the significances of systolic murmurs after World War I, when none were considered important, is now settling to a reasonable middle ground.

At a convalescent center of the Army Air Force for rheumatic fever in Florida, Robertson and his associates[27] studied the anxiety neuroses in patients with rheumatic fever and concluded that they were fostered by the preceding therapeutic program which demanded absolute bed rest throughout and even beyond the acute stage of the disease. They challenged the concept that *confinement to bed* implies the ultimate expression of rest. They defined rest as "maximum ease and comfort, physically, mentally and emotionally. Bed rest ceases to be rest when the patient is no longer at optimum comfort in his environment."

A group of 100 patients in the acute phase of the disease were permitted to sit in or out of bed and to walk a short distance to the latrine. The presence of joint symptoms, of changing cardiac murmurs, of varying P-R intervals, of increased erythro-

cyte sedimentation rates and of other signs of infection were not considered deterrents to this limited physical activity. The only exception were patients with heart failure or with incapacitating joint inflammations.

Results are admittedly difficult to evaluate but these patients, in contrast to a group observed the previous year, slept soundly, their appetites were better as reflected by gains in weight, their bowel habits were more regular and their morale for recovery was improved. During the early period of limited physical activity they were taking therapeutic doses of salicylates. The clinical and laboratory phenomena indicative of active rheumatic processes diminished as rapidly as in the previous year when strict bed confinement was practiced. At the end of six months no soldier of this group had to be discharged because of an anxiety neurosis.

This study was made in a group of young men. The findings cannot be applied unqualifiedly to children, especially those below the age of puberty, which is the most serious period both as far as recurrences and development of permanent heart disease are concerned. I would urge you, however, to consider what you mean by rest. I believe that often a child may be more quiet if allowed to sit in a chair but I also realize that it is an individual behavior problem. It is regrettable that more beds are not available in convalescent hospitals for rheumatic children. When the period of rheumatic activity is prolonged, satisfactory management at home, especially if there are normal siblings present, is virtually impossible. The same advantages that obtain in a tuberculosis sanatorium, namely, of being placed with others in the same stage of the disease, of being under the care of those specially interested in their problems and finally of obtaining a true perspective of the disease in relation to future physical activities, should be secured. While one should be more conservative in young children, it is the *factor of infection* and not *overactivity* that sends these children into heart failure and an early demise.[28]

Drug therapy is entirely symptomatic. Penicillin,[29] like the sulfonamides,[30] is of no value in the acute attack and may even be dangerous.

Salicylates in varied forms, dosages and methods of administration were used extensively in the Army and Navy. The hope that large doses would prevent the development of cardiac damage has not materialized.[30] In fact it has been shown that large doses, especially if given intravenously, produce serious and dramatic toxic effects. The dose of salicylates should be sufficient to control the patient's symptoms and to relieve the exudative phenomena of the disease. Larger doses than this are of no proven value.[32] Extremely large doses (over 10 Gm. daily) intravenously or orally may be dangerous in adults.[33] In children the danger seems equally great and deaths have been reported.[34]

The use of sulfonamides as a prophylactic measure is now limited by the presence of hemolytic streptococci which are resistant to the action of all such drugs. Once a patient has recovered from the acute phase, the most serious threat to his well-being is a recurrent attack. Recurrences are more frequent in children but may occur at any age. They are more apt to occur, however, within the first three years of the initial attack.[35] The risk of heart disease or further damage to the heart exists with each recurrence.

I would consider it advisable in selected cases to use these drugs prophylactically against hemolytic streptococcic infections. The usual precautions against toxic reaction must be taken. Care must be taken that sulfa-reactions are not treated with more sulfa, through ignorance on the part of one physician that sulfonamides were

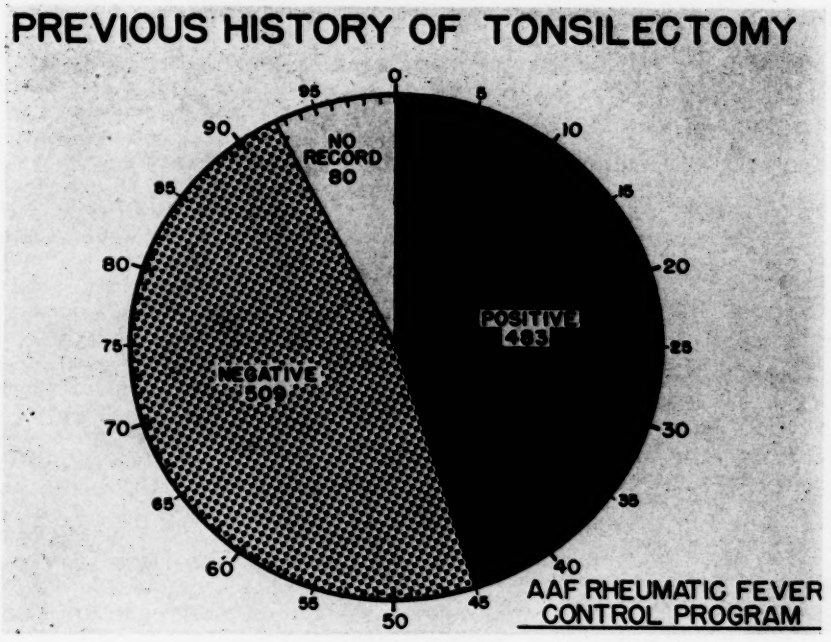

FIG. 3

being administered. Sulfonamide-resistant stains of Group A streptococci can cause infections which are followed by rheumatic fever.

The use of penicillin for prophylactic purposes, now that oral preparations are available, has not been investigated sufficiently to warrant any definite statement at this time.

The value of tonsillectomy in preventing recurrences of rheumatic fever has been disproven. Figure 3, taken from a study of over a thousand cases in the Army Air Forces, illustrates the relationship of an attack of the disease to the history of a previous tonsillectomy. The figure does not show a breakdown of the cases of rheumatic fever as regards initial or recurrent attacks.

SUMMARY

The importance of rheumatic fever as a chronic disease and many of the epidemiological factors, especially the relationship to hemolytic streptococcal infections, were discussed.

Variations in signs and symptoms in different age groups and in different environments often make recognition of the rheumatic fever syndrome difficult. The presence of carditis, particularly in association with other major and minor manifestations of the disease, gives valuable contributory evidence.

Rheumatic valvular heart disease in children and young adults rarely requires active treatment unless rheumatic infection is also present. It is the activity of the infection, especially in the myocardium, that gives rise to cardiac symptoms and interferes with the efficiency of the heart.

The treatment of an acute attack is purely symptomatic. Massive doses of salicylates, sulfonamides and penicillin are of no proven value. Salicylates in amounts sufficient to control symptoms and to relieve the exudative phenomena of the disease are the most satisfactory and the least dangerous form of therapy.

The management of acute rheumatic fever presents two additional problems: (1) the prevention of recurrences, and (2) the prevention of cardiac neuroses.

The use of sulfonamides to prevent streptococcal infections is less effective because of

sulfonamide-resistant strains of these bacteria. The value of penicillin prophylaxis must be investigated. Tonsillectomy has no specific benefit in this regard.

Cardiac neuroses may be engendered by prolonged bed rest and constant attention to the heart. The value of strict bed rest may justifiably be questioned; but in the pre-pubescent child, because of the more serious potentialities of the disease, greater caution in permitting physical activity would seem advisable. The establishment of more convalescent facilities would do much to solve this problem.

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Industrial Exposures to Chlorinated Hydrocarbons*

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THE substitution of chlorine atoms for hydrogen atoms in the fatty series of methane, ethane and ethylene forms valuable solvents that are used extensively in industry. All of the chlorinated hydrocarbons are a potential hazard to the health of the worker. Human beings should not be exposed to atmosphere in which the odor of chloro-hydrocarbons is detectable. The ability to detect the presence of the compound in the air by the sense of smell indicates that the amount present is above the safe limit of exposure. They, as a class, are more toxic than the solvents that contain no chlorine.

Chlorinated compounds as a rule are more readily absorbed through the skin than are the original substances free of halogen. Because of this property, intoxication may take place by absorption through the skin as well as by inhalation of the fumes. Intoxication through skin absorption is comparatively rare in industry. However, they may cause a dermatosis as they dissolve the natural fats and oils of the skin thereby causing a dryness and a scaling. In the more severe cases vesiculation is frequently seen.

Nerve endings in the skin and mucous membrane may be injured by the solvents. An example of this is seen in the action of trichlorethylene on the fifth cranial nerve. A case of carbon tetrachloride polyneuritis[1] has recently been reported as being due to absorption through the skin.

Because of the possibility of dermatosis and systemic conditions arising because of skin absorption, the employees should be warned to keep their hands out of the solvents and to wash off any spillage that may occur while handling the solvents.

The chlorinated compounds may cause injury to the liver and kidney if there is exposure to the fumes over a long period of time. Because of this tendency to cause liver and kidney damage, pre-placement examination should rule out alcoholics, obese persons and those with a previous history of some liver disease or treatment with arsenicals. There are some indications that a person whose blood shows a low calcium content should also be eliminated.

Liver damage may be detected by palpation of the organ, by the various liver function tests and by an indication of jaundice. Unfortunately, it is frequently hard to evaluate the blood findings in cases of liver damage. This is especially true of chlorinated naphthalene intoxication. It has been observed that among the first symptoms noted are nausea, loss of appetite, vomiting, abdominal pain, constipation or diarrhea, headache and a feeling of fatigue.

It is a safe rule to follow that if an employee working with chlorinated hydrocarbons comes to the First Aid Room complaining of any of these symptoms that he should be taken away from the exposure and watched carefully. It has been my observation that if this is done, especially in cases of exposure to chlorinated naph-

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thalene, the man recovers completely. On the other hand, if we waited until the blood findings were positive as to liver damage, it was frequently too late.

Carbon tetrachloride and trichlorethylene have been used for many years in industry. Carbon tetrachloride is a cheap, non-inflammable solvent and its use is increasing for extinguishing fires, dry cleaning, degreasing and extraction of fats. Its effects on the human system have been observed for many years. Our early knowledge of its action on humans was first obtained by its therapeutic use as an anthelmintic.

Its entrance into the body is generally by inhalation during an industrial exposure. The absorption from the lungs is rapid at the beginning and then more slowly. In six hours after removal from the exposure 78.7 per cent is eliminated through the lungs. Robbins reports that large quantities are found in the bone marrow, in the liver and in the bone.

The blood picture does not reveal the damage that is done to the system. Smyth and Smyth from their work believe that the earliest possible information was obtained by the determination of the icteric index, blood calcium, visual fields and van den Bergh reaction. However, the subjective symptoms such as nausea, vomiting, headaches and abdominal sensations previously mentioned in connection with chlorinated compounds should be taken into consideration. There is a question in the minds of some as to the importance of blood calcium in cases of carbon tetrachloride poisoning. Minot found that a person with low blood calcium was susceptible to intoxication when carbon tetrachloride was used as an anthelmintic.

Experience has indicated that because carbon tetrachloride is a depressant to the heart muscle and disturbing to conduction, pre-placement examination should exclude anyone with a heart disorder.

It has been the opinion for some time that 100 parts per million of carbon tetrachloride was a safe limit in the atmosphere of a shop. This question of permissible limits is very important. Concentrations within a permissible limit indicate only that at the particular time at which the sample was taken the air sample was within this limit, without indicating the maximum air content during the day or how often or for how long the permissible limits are exceeded. The engineer in designing his ventilating system should have determined the air contents throughout the whole day and for several days in the winter and summer months. Having this information, he can then plan the ventilation so that under the worst conditions the atmosphere of the shop will never exceed the permissible limit.

The Bureaus of Industrial Hygiene of several states have been claiming that 100 parts per million was too high a concentration for carbon tetrachloride and that the permissible limit should not be above 50 parts per million.

A careful study of one of these publications indicates a lack of information necessary to arrive at a scientifically justified conclusion. Nausea was reported when the concentration was below 25 parts per million. At the same time it was recorded that the air sample was taken after improvements had been made and in the neighborhood of the worker. It should be noted that these observations were made in a textile industry where the worker is engaged in work in which he tends to lean over the material. It would have been very interesting and valuable if the determinations had been made at the exact level of the worker while the work was being carried on and at the time he was leaning over the cloth.

The importance of these observations is shown in a survey made by Harris, Ford, Patty and Hatch on trichlorethylene de-

greasing tanks summarized in the following table:

Plant No.	Breathing Zone ppm.	General Room Air ppm.
6B	500	290
15D	290	230
10D	500	100
13D	340	80
13D	400	20
19D	60	0

In spite of this criticism of the data furnished in this report, I am inclined to think that it is well to place the permissible limit at 50 p.p.m. for carbon tetrachloride. My reason for this stand is that many times the shop puts a strain on the ventilating system as business increases. While the contents for the atmosphere may have been low when the system was first put into operation, changes may have taken place as a result of expansion and accidents do occur.

There is evidence that persons build up an immunity to carbon tetrachloride. This suggestion is confirmed by animal work by Smyth and Smyth who found that regeneration occurred in the liver of exposed animals and that these new cells were more resistant to the solvent.

Trichlorethylene is a powerful narcotic. Liver and kidney lesions are practically unknown from this exposure among industrial workers. Usually on autopsy only an acute congestion of all of the internal organs is found. A few investigations of the blood picture of men exposed to the solvent showed no abnormal conditions. Recent animal work in which dogs were used shows that with large doses it may cause liver damage.

Trichlorethylene volatilizes easily and has an agreeable odor. Under the influence of light and heat it is decomposed into phosgene, hydrochloric acid and carbon monoxide. Most of the deaths reported in the European literature are due to the formation of phosgene.

The workmen are known to become addicted to the fumes and they tend to gather where the fumes are being given off. The effects depend on the concentration of the fumes. They first experience a sweet taste in the mouth, singing in the ears, a dulling of sight and hearing, a state of euphoria and a delightful desire for sleep. If exposure continues, unconsciousness and death supervene.

Very few cases of trichlorethylene intoxication are reported in the American literature. This is probably because we are aware of the hazard connected with its use in cleaning and degreasing metal articles as well as when extracting fats and oils from animal and vegetable matter. American industry as a whole employs the enclosed system in this type of work. The tendency to heat up the solvent during the operation will of course increase the possible hazard from the fumes.

Trichlorethylene can be absorbed through the skin as well as by inhalation. About 72 per cent of the fumes inhaled are absorbed from the lungs. It is by no means a nontoxic material and extreme care should be taken in its use. It has been suggested that long continued exposure may be held responsible for lesions in the optic and trigeminal nerve with complete blindness resulting in several cases. McConnell calls it a nerve poison.

Two hundred p.p.m. of trichlorethylene are considered the permissible limit in the atmosphere. Some states have placed it as low as 100 p.p.m. The manufacturers remove the impurities and add volatile stabilizers which permit its use in the presence or absence of air, water, light and any of the common construction metals and any temperature up to 120°c. The object of this is to prevent the formation of phosgene when exposed to these conditions.

At higher temperatures, such as occur in gas flames, electric heaters and burning tobacco, chlorinated hydrocarbon vapors may decompose with the formation of toxic and corrosive substances (DuPont).

Chloroprene is used extensively in the chemical industry and is the starting point for the synthetic rubber "Duprene." Work at the Haskell Laboratory has given us the best data on this compound. It causes a depression of the central nervous system and damages the vital organs, causing injury to the liver and kidneys. It can be absorbed through the skin with systemic effects. When inhaled, a primary irritation of the respiratory tract occurs, followed by progressive depression of the respiration and asphyxia. A fall in the blood pressure occurs. It is not settled as to whether this is due to dilatation of the splanchnic blood vessels or to a direct depressant action on the heart. Its effects are not apparent in the blood picture although anemia has been reported. The Haskell Laboratory found that chloroprene causes degenerative changes in the male reproductive organs. It is a very toxic compound and must be handled in a careful manner. A concentration of 0.3 mg. per liter of chloroprene in the atmosphere may cause toxic symptoms. "The medical man should examine the employee at frequent intervals. The icteric index of the blood should be determined at these intervals, and the urine should be tested for albumin, reducing substances and bile pigments. Frequent determinations of the blood pressure may be advisable; low blood pressure should be considered as indicative of possible incipient poisoning as should also complaints of loss of appetite, indigestion, and catarrhal conditions of the respiratory tract."

Dichloromethane (methylene chloride) is, from experimental and industrial observations, a compound that has the lowest toxicity among the halogenated hydrocarbon solvents. It should not be confused with methyl chloride which has been used as a refrigerant. Methylene chloride is being used more and more as a solvent for resins, fats, oils and rubber. It has also been used as a paint remover. The concentrations in the air necessary to cause acute poisoning are relatively high, ranging from 14,000 p.p.m. for two hours' exposure to 50,000 p.p.m. for one hour. Narcosis is not evident in exposures that are found in industry, and no abnormalities are found in the blood and urine. Mild incoordination and ataxia are seen in animals. There is no apparent liver damage. It has been suggested that 500 p.p.m. is the permissible limit. The effects that have been noticed in humans have been laid to the impurities that may be present. Heppel and Neal[2] found that the running period of rats exposed to 5,000 p.p.m. suffered a great reduction as measured in a standard type of revolving drum.

Vinyl chloride reacts in a somewhat similar manner. It is of very low toxicity and has been used as a solvent for resinous compounds. It has narcotic properties. It is suggested that because of this property accidents may occur more frequently with both of these solvents if the employee is exposed to a high concentration and yet not high enough to cause noticeable narcosis. This might be explained by the increase in reaction time similar to that claimed as resulting from exposure to toluene. I have seen incidents that support this theory in the case of vinyl chloride but have not been in a position where I could make similar observations on methylene chloride.

Chlorinated naphthalenes have aroused considerable interest since the first World War. They are not solvents but are waxes which have been used extensively in the electrical industry for insulation purposes. They are non-inflammable and for this reason have been used extensively in coating wire for airplanes and warships.

Chlorinated naphthalenes as used in the industry are not pure chemical compounds but mixtures of tetra, penta and hexa chlornaphthalenes. In the industry for many years they were known in Europe as "Perna" and in this country as "Halowax" and "Haftax." Unfortunately, these terms were not definitely restricted to the compound and might be used for other substances. They were simply trade names. They were frequently confused with chlorinated diphenyl.

These chlorinated compounds have a melting point ranging from 117°C. to 132°C., depending upon the mixture. There are two methods used in impregnating the wire, the hot and the cold. Many persons demanded the hot treatment method. This method consists of drawing the wire covered with asbestos thread through a bath of melted chlorinated naphthalene. As the wire leaves the bath it is drawn through a die to remove the excess impregnating material from the wire. Coal, oil or the electric current may be used to heat the bath. The object is to have the temperature of the material raised to a little above the melting point and just sufficiently high to permit the impregnation of the asbestos coating. Unfortunately, it is hard to control the temperature by heating with coal or oil. Absolute control is possible by means of electricity.

The cold method consists in dissolving the naphthalene compound in toluol and then driving off the toluol by either infrared lamps or in an oven. The cold method is probably the safer of the two methods.

The hot method can be handled in a safe manner if each impregnating machine is enclosed and control of the ventilation is so managed that when the door is opened the speed of the ventilating fan is increased so that the suction will take care of the fumes that would otherwise be allowed to escape into the atmosphere. One great source of danger was the tendency of the employees to dump the hot material on the floor at their feet when cleaning out the vat. Covered cans were furnished them but even then the covers were not used.

Besides the use of chlorinated naphthalene in the wire industry it is used to impregnate condensers and similar apparatus in the electrical industry.

Dermatological complaints are very common among workers engaged in occupations using chlorinated naphthalenes. It has been found that in plants which are not careful in the handling of this material, at least 50 per cent of the exposed persons develop dermatitis. The chloronaphthalenes must be present in a finely divided condition in order to cause acne. This very finely divided state permits a thin layer to form on the skin, clogs the pores and results in papules. It seems likely that the action of the wax produces a hyperkeratosis in the lining of the follicles of the skin, thereby causing an obstruction; and the obstructed follicle may contain organisms which will produce a secondary infection resulting in pustules, etc. Undoubtedly, the wax initially plugs the pore and it may be that some of the pustules do arise from a deeper penetration of this wax, but in most cases it is believed that obstruction is due to thickening of the epithelium lining the follicle. Persons handling the cold wax blocks do not develop dermatitis. In the hot process, a considerable quantity of the finely divided sublimate is formed, and care must be taken not to have the ventilating vents choked up by the deposits.

The eruptions are found principally on the face and neck. Comedos frequently first appear back of the ears. The forehead, cheeks and chin are most often involved. The nose is very seldom affected. The rubbing of the shirtband appears to aid in its appearance on the neck. For a good

discussion of the acne I would recommend the article by Jones.[3]

The use of face cream is not advisable. In the first place, it gives a false sense of protection. In the second place, I have never seen it applied by the men in a manner to give the protection it is supposed to give. Generally it is simply daubed on and remains in streaks.

Cleanliness is the best preventive measure on the part of the employee. Unfortunately, the wax is difficult to remove from the skin and the ordinary soaps do not clean the skin in the proper manner. Soaps made from sulfonated oils are the best ones to use in the plant. Some persons believe that powdered soaps containing a corn meal abrasive are quite effective for this purpose and are preferred to the sulfonated oils. Even if good soaps and warm water are provided, one must educate the worker to wash behind the ears and the neck as well as the face. In any case, the cleansing must be very thorough or it will not be effective.

Eruptions do occur on other parts of the body. This is generally due to impregnation of the clothes with the wax and then having the clothes rub the irritating material into the skin. Because of this fact frequent changes of overalls that have been starched to make them less permeable to the wax is to be recommended. Full length underwear with long sleeves should be worn and changed twice a week.

A pre-employment examination should rule out all persons with an oily skin, established acne or seborrhea. No one who has worked with other chlorinated hydrocarbons, such as carbon tetrachloride that affects the liver, should be permitted to work in this industry. I repeat that preplacement examination should rule out alcoholics, obese persons, and those with a previous history of some liver or kidney ailment or of treatment with arsenicals.

My experience has indicated that if all of these precautions—ventilation, good housekeeping and personal cleanliness—are observed the number of new cases that occur will be cut down to a minimum. Where twenty to thirty new cases occurred a month, only one or two showed up in six months.

It is interesting to note that regular skin tests for dermatitis on albino rabbits are a failure with compounds of this nature. It is only when one uses Dr. Irish's method of treating the inside of the rabbit's ear that the skin conditions develop. This has been my experience both with the chloronaphthalene and chlorodiphenyl products.

In proportion to the number exposed to the fumes of chlorinated naphthalene only very few have developed fatal liver damage. The autopsies reveal a damaged liver with the characteristics of yellow atrophy. There are some that have shown by laboratory and clinical tests that the liver had been slightly damaged. These last cases probably are similar to liver damage found in animals that had been exposed to small amounts of the fumes but at autopsy, when killed for examination, show that regeneration had taken place. Other organs are not generally affected. The symptoms of the fatal cases follow a regular pattern. The first symptoms noted by the affected employees were a "rundown" condition and jaundice. As the jaundice increased there appeared an increase in general malaise, anorexia, attacks of dizziness, loss of weight and a tendency to vomit. Severe abdominal pains across the upper quadrant were noted. The blood picture was normal except for a low or low normal blood sugar. Again I emphasize the necessity for caution when a man complains of nausea, loss of appetite, vomiting, abdominal pains, constipation or diarrhea, headache and a feeling of fatigue.

The question has arisen many times as to whether the systemic symptoms are the result of absorption through the skin. My

observations around plants lead me to doubt if skin absorption was the etiological factor in the liver damage.

Animal experiments have shown that if the wax is dissolved in oil and applied to the skin over a long period of time absorption does take place and slight liver damage may occur. Also, if the wax is applied to a broken or damaged skin over a period of months, similar absorption can take place.

It would seem that the liver injury cases that have arisen are due to inhalation of the fumes in plants where proper care was not taken. Furthermore, the men affected probably had some liver injury before employment. As has been said, it is not always possible to detect a slightly damaged liver in a preplacement examination, nor do the men always give a correct history of their previous work.

Skin disorders have been found among electricians. These may result from fumes during the soldering of wire or from the fine dust which occurs when the wire is scraped to present a clean surface. But while skin conditions have been reported, I do not know of any liver cases that have resulted from this type of work.

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Seminar on Antibiotics

The Current Status of Calcium Penicillin in Beeswax and Peanut Oil*

Data from a Study of 600 Cases and Clinical Observation of 4,000 Patients Given 60,000 Injections

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SINCE the initiation of penicillin therapy, one handicap in administration has been apparent. This has been the necessity for injections of penicillin in aqueous solution approximately every three hours in order to maintain effective therapeutic levels in the blood. In addition, the latter fact has often necessitated hospitalization of patients in order to provide the full benefits of this drug.

In previous reports[1,2,3,4] we have given the background and the progress made in the development of calcium penicillin in beeswax and peanut oil. It was demonstrated that of the numerous combinations tested in order to prolong the action of penicillin, none from a practical standpoint was successful except the combination of calcium penicillin in beeswax and peanut oil. The standard preparation[4] which would maintain therapeutic levels for approximately twenty-four hours after a single injection is 300,000 units of amorphous calcium penicillin in 4.8 per cent beeswax (by wt.) in peanut oil contained in 1 cc. (Hereafter, in this manuscript this mixture will be referred to as P.O.B.)

This report covers a period from September, 1944, through August, 1946. The data were accumulated in two periods of time: the first, a study group of 600 cases under complete observation (shown in Tables I to VI), hospitalized and ambulatory, who were observed from September, 1944, through August, 1945; the second, clinical observations of approximately 4,000 patients with all types of infections who received as routine penicillin therapy a total of about 60,000 intramuscular injections of P.O.B. from September, 1945, through August, 1946. Since September, 1945, all patients at Walter Reed General Hospital requiring penicillin therapy have received P.O.B.

It will be noted in the tables that a considerable number of patients were given less than the recommended single dose of 300,000 units in 1 cc. These individuals were of two groups: the first, those who were treated in the period before it was possible to prepare a suspension of 300,000 units of calcium penicillin in 4.8 per cent beeswax (by wt.) in peanut oil contained in 1 cc.; the second, the group who received their dose of penicillin based on units per pound. In this

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group 3,000 units per pound was given to those weighing up to 100 pounds, 300,000 units for those weighing between 100 and 200 pounds, and 600,000 units for those over 200 pounds.

single injection of calcium penicillin in beeswax and peanut oil was as successful as multiple injections of penicillin in aqueous solution. The successful treatment of 175 cases of uncomplicated gonorrhea in males

TABLE I

TREATMENT OF GONORRHEA WITH A SINGLE INTRAMUSCULAR INJECTION OF CALCIUM PENICILLIN IN BEESWAX AND PEANUT OIL

Total Cases—331 Cure rate with 300,000 units of calcium penicillin in beeswax and peanut oil—98%

	Single Dose (Oxford Units)	No. of Cases	Males		Females		Previous Treatment		
			White	Negro	White	Negro	None	Sulfonamide	
Group I	150,000	34	19	13	1	1	32	Males W/1	Males N/I
	Failures—4								
	Males* White 1	Males* Negro 1	Females† White 1	Females† Negro 1					
	* Failures cured with second single injection of 300,000 units of P.O.B. † Failures cured with second single injection of 150,000 units of P.O.B.								
Group II	200,000	21	6	6	6	3	20		1
	Failures—1* * Cured with second single injection of 200,000 units of P.O.B.								
Group III	250,000	8	4	3	1	0	7		1
	Failures—0								
Group IV	300,000 (in 4.8% Beeswax (by wt.) in Peanut Oil contained in 1 cc)	268	115	130*	14	9	260	6	2
	Failures—4* * Question as to relapse or reinfection: cured with second single injection of 300,000 units of P.O.B.								

Epididymitis—Cases . . . 2
1 treated with 5 single daily doses of 300,000 . . . . 1,500,000 P.O.B.
1 treated with 4 single daily doses of 300,000 . . . . 1,200,000 P.O.B.

P.O.B.—Penicillin in Beeswax and Peanut Oil

GONOCOCCAL INFECTIONS

The initial satisfactory clinical results with this mixture were in the treatment of acute uncomplicated gonorrhea[2] in which a

by a single intramuscular injection of 100,000 and 150,000 units of P.O.B. has already been recorded.[3] Successful results have also been reported subsequently by others utiliz-

ing the same method of administration.[5,6] Since the above report[3] of the treatment of 175 cases of gonorrhea, an additional 331 cases have been treated by a single injection of the same mixture with the dosage range as shown in Table I. This table shows not only the dose administered but also race, sex, previous therapy if any, and complications. The criteria of cure in males are similar to those already reported.[3] However, in the female cases, three smears and cultures were taken, the last being obtained in the third week following therapy. The four cases in Table I which had received an injection of 300,000 units and required a second single injection of the same dose were difficult to evaluate as to whether they were relapses or reinfections. From the history obtained, either was possible. Even considering these four cases as failures, the cure rate after a single injection of 300,000 units of P.O.B. is approximately 98 per cent. Therefore, a single injection of 300,000 units in 4.8 per cent beeswax and peanut oil contained in 1 cc. is adequate for uncomplicated gonorrhea.

The two cases of epididymitis also noted in Table I responded to treatment in four to five days. Several cases of acute prostatitis have responded successfully to single daily injections of 300,000 units of P.O.B. for four to six days.

In no instance has there been any evidence of the gonococcus being resistant to penicillin nor have there been any cases showing acquired resistance. Over 100 strains of gonococci have been tested for *in vitro* sensitivity to penicillin (primarily G). Eighty per cent of these were sensitive to 0.02 Oxford units per cc. In the cases noted above in which more than one injection was necessary, no change in *in vitro* sensitivity of the organism occurred after the initial injection. For one gonococcal strain 0.3 Oxford units per cc. was necessary *in vitro;* however, this case responded to a single injection of 300,000 units of P.O.B.

MENINGOCOCCAL INFECTIONS

For meningococcal meningitis the drug of choice appears to be sulfadiazine. However, if it is to be supplemented or replaced by penicillin, 300,000 units or more of P.O.B. at twelve-hour intervals is advisable. In addition, the intrathecal administration of penicillin in aqueous solution should be administered.

No patients with the meningococcic blood infection were treated. However, the amount of P.O.B. given parenterally which would be desired would appear to be that indicated in the foregoing paragraph.

PNEUMOCOCCAL INFECTIONS

A total of forty-two cases of pneumococcal pneumonia were treated by single daily injections of P.O.B. These, as shown in Table II, were in the study group. In addition, a considerable number have been treated in the same fashion in routine therapy in the hospital. Typing of the sputum for pneumococcus, roentgenograms of the chest, blood cultures and hematological study were all accomplished prior to therapy to verify the diagnosis of pneumococcal pneumonia. All cases were lobar pneumonia unless otherwise indicated. Table II shows the number of single daily doses, quantity of penicillin required, distribution of cases as regards age and sex, type of pneumococcus and the results. As shown in Table II, four cases had positive blood cultures. The average *in vitro* susceptibility to penicillin (primarily G) of thirty strains of pneumococci which have been studied is 0.04 Oxford units per cc. In this group of forty-two cases, none died nor were there any cases of empyema. Of the forty-two cases, thirty-eight required only four days of treatment. Except for the group of sixteen who received only a single

TABLE II

PNEUMOCOCCAL PNEUMONIA—TREATED BY A SINGLE DAILY INTRAMUSCULAR INJECTION OF CALCIUM PENICILLIN IN BEESWAX AND PEANUT OIL.

42 CASES

No. Single Daily Doses Penicillin	Total Cases	No. of Cases	Sex		Single Daily dose Penicillin X 1000	Total Units X 1000	Pneumococcus Type	Blood Culture	Remarks
			M	F					
1	16	2	2 A		100		VIII, XI	Neg.	Results satisfactory in all cases unless otherwise stated.
		1	1 C		120		—		
		3	2A	1C	150		II, —	Neg.	
		1		1A	175		XX	Neg.	
		3	3A		200		II, VIII, XII	Neg.	
		6	6A		300		I, III, —	Neg.	
2	9	1	1 I		20	40			* Treated early in development of calcium penicillin in beeswax and peanut oil—after two days placed on sulfadiazine due to temperature not subsiding entirely to normal. Probably would have responded to penicillin if continued for sufficient period of time.
		1	1 I		60	120			
		1	1 I		100	200			
		4	2 A*	1 A	150	300	V, —, —	Neg.	
				1 C†					
		1	1 A		200	400	—	Neg.	
		1	1 A		300	600	—	Neg.	
3	6	2	2 A		100 & 150(2)	400	III, VII	Neg.	† Bronchial pneumonia.
		1		1 A	150 & 200(2)	550	I	Pos.	
		1		1 A	150	450	I	Pos.	
		1	1 A		200	600	VIII	Neg.	
		1		1 A	300	900	—	Neg.	
4	7	2	1 I	1 I	80	320			
		1	1 C		100	400			
		1	1 A		100 & 150(3)	550	XXV	Neg.	
		3	3 A		200	800	—, VII, III	VII Pos.	
5	1	1		1 A‡	150(2) & 200(3)	900	II	Pos.	‡ 76 years of age. Moderate cardiac decompensation—responded excellently to treatment shown even though bacteremia present. Temperature subsiding by the third day.
6	2	1	1 C†		40 & 60(5)	340 340			
		1		1 A	300	1,800	—	—	
7	1	1	1 A		300	2,100	—	Neg.	

Pos.—Positive. Neg.—Negative. A—Adults above 16 years. C—Children 1 to 16 years. I—Infants to 1 year.
——No type obtained. No development of empyema in this group of cases. No deaths.

Standard material for single 24 hour dose, 300,000 units calcium penicillin in 4.8% beeswax and peanut oil contained in 1 cc—other doses noted in table for adults represent mixture used in process of development of the standard material.

Preferred plan of therapy: Single daily dose—3,000 units per lb. up to 100 lbs. 300,000 units 100—200 lbs. 600,000 units above 200 lbs.

injection, P.O.B. was given routinely for one additional day after the temperature had subsided to normal. It is also noted in Table II that there were two patients who were given a single daily injection of 150,000 units for two days without subsidence of the temperature. At this time the P.O.B. was discontinued and sulfadiazine was initiated with complete recovery. This occurred during the early development of P.O.B. and it is quite likely that if P.O.B. at the standard dose of 300,000 units had been continued for a longer period of time, the results would have been satisfactory.

In the routine therapy in the hospital which has been carried out with P.O.B., pneumococcal pneumonia, empyema and other infections due to the pneumococcus have been treated by single daily doses of 300,000 units of P.O.B. The total duration of therapy is dependent upon the individual case. For overwhelming pneumococcal infections, it is advisable to give 300,000 units or more of P.O.B. at twelve-hour intervals. As shown previously,[4] this dose will maintain constant levels of 0.6 to 1.25 Oxford units per cc. or higher in the blood.

For pneumococcal meningitis, a minimum of 300,000 units of P.O.B. or more should be given at twelve-hour intervals, plus sulfadiazine with levels of 18 to 20 mg. per 100 cc. in the blood. Treatment otherwise, including intrathecal administration of penicillin in aqueous solution, is the same as previously employed.

STAPHYLOCOCCAL INFECTIONS

A total of ninety-three cases due to Staphylococcus aureus was observed in the study group. As shown in Table III, these include forty-eight furuncles, twenty-seven with furunculosis, ten with carbuncles, eight with abscesses (location as shown) and one with subdural abscess with severe bacteremia. Table III also shows the schedule of therapy for these cases including the amount of a single dose, number of days of therapy, total dose of penicillin and results.

The furuncles responded rapidly with the single daily dose of P.O.B. which was given; surgical drainage rarely was necessary. As a rule spontaneous evacuation of the pus occurred within the first forty-eight hours or resolution without drainage. The latter tended to occur if treatment was instituted within the first twenty-four hours after the initial appearance of the lesion. It was also obvious that the earlier the treatment was instituted, not only was the response more rapid, but the duration of treatment was less. This is shown in Table III by the thirty-eight patients who received one to three injections. They were seen within the first forty-eight hours of the appearance of their furuncle.

The response to P.O.B. of the twenty-seven patients with furunculosis was as satisfactory as those who had individual furuncles. In general, the duration of treatment was longer. The use of P.O.B. in cases with recurrent furuncles or furunculosis did not tend to prevent recurrences but definitely shortened the course of the condition.

The ten patients with carbuncles also responded excellently to the single daily injections of P.O.B. In the period of twenty-four to thirty-six hours following initiation of treatment there tended to be induration around the site of the carbuncle with increased pain. The patients usually had a slight degree of fever and showed evidence of toxic reaction. Shortly thereafter, rapid regression of the lesion occurred with spontaneous evacuation of the pus and relief from pain. In only two instances was it necessary to incise and drain the lesions.

Four patients with breast abscess were treated as shown in Table III. One, an infant one month of age, responded to three injections of 100,000 units of P.O.B. with spontaneous evacuation of the pus occurring

TABLE III

STAPHYLOCOCCAL INFECTIONS—93 CASES

TREATED BY A SINGLE DAILY INTRAMUSCULAR INJECTION OF CALCIUM PENICILLIN IN BEESWAX AND PEANUT OIL

No. Single Daily Doses Penicillin	Total Cases	Sex		Range of Single Daily Dose Penicillin (x 1000)	Range of Total Units (x 1000)	Remarks
		M	F			
Furuncles—48 Cases						
1	13	1 I 9 A	1 C 2 A	20–300	20–300	Results satisfactory in all cases unless otherwise stated.
2	12	7 A	3 A, 2 C	90–300	180–600	
3	13	8 A	3 A, 2 C	60–300	180–900	
4	6	1 A	4 A, 1 C	50–300	200–1,200	
5	1	1 A		300	1,500	
6	1	1 A		300	1,800	
7	1	1 A		150	1,050	
8	1	1 A		2–150, 1–200 5–300	2,000	
Furunculosis—27 Cases						
1	3	2 A	1 A	300	300	* One child had recurrence short period after treatment and given 3 doses of 300,000 units with satisfactory results.
2	5	3 A	1 C, 1 A	90–300	190–600	
3	5	1 C, 1 A, 1 I		90–300	270–900	
4	7	2 C*, 2 A	3 A	150–300	600–1,200	
5	4	2 A, 1 C	1 C	150–300	750–1,500	
6	2	1 A	1 C	300	1,800	
9	1	1 A		300	2,700	
Carbuncles—10 Cases						
1	2	2 A		150–200	150–200	A toxic reaction apt to occur 24 hours after initiation of treatment; possibly due to destruction of bacteria.
2	3	1 A	2 A	150–300	350–600	
3	2	2 A		300	900	
4	1		1 A	2–150–2–200	700	
6	1		1 A	300	1,800	
8	1	1 A		300	2,400	
Abscesses—8 Cases						
1	1	1 C (Rectal)		150	150	
3	2	1 I (Breast) 1 A (Anal)		100–300	300–900	
4	3		1 A (Perineal) 2 A (Breast)	150–300	900–1,200	
6	1		1 A (Breast)	300	1,800	
Subdural Abscess† (Bacteremia)						
8	1		1 A	1–200–7–300	2,300	See text

A—Adults above 16 years. C—Children 1 to 16 years. I—Infants to 1 year.

Standard material for single 24 hour dose, 300,000 units calcium penicillin in 4.8% beeswax and peanut oil contained in 1 cc—other doses noted in table represent mixture used in process of development of the standard material.

Preferred plan of therapy: Single daily dose—3,000 units per lb. up to 100 lbs. 300,000 units 100–200 lbs. 600,000 units above 200 lbs.

twenty-four hours after the first treatment. Two cases occurred during the postpartum period, both of which responded to four single daily injections of 300,000 units. These breast abscesses resolved without drainage, probably because treatment was initiated almost as soon as the condition occurred. The fourth case was in an unmarried female (age twenty-one) who required six injections of 300,000 units. Incision and drainage were also necessary with the final result satisfactory.

Early acute osteomyelitis due to hemolytic staphylococcus aureus has been treated with single daily doses of 300,000 units of P.O.B. Four cases have responded satisfactorily without surgical intervention being necessary. This was probably due to the early initiation of therapy. Chronic cases have also been treated with P.O.B. but, as has been shown previously,[7] surgical procedures have been required despite the administration of penicillin.

The case of subdural abscess with a blood culture strongly positive with hemolytic staphylococcus aureus (susceptible *in vitro* to 0.08 Oxford units per cc.) was that of a twenty-two-year old female who was admitted to the hospital in a practically moribund state with a temperature of 103.5°F. She was immediately given a single injection of 200,000 units of P.O.B. and surgical drainage was instituted. She then received 300,000 units of P.O.B. daily for a total of seven more days. By the forty-eighth hour after the initiation of therapy the temperature had subsided to normal and continued so with the patient making a complete recovery. Although surgical drainage was accomplished in this case, it is doubtful whether she would have survived without the use of penicillin.

The average range of *in vitro* susceptibility to penicillin of 122 strains of hemolytic staphylococcus aureus was 0.08 to 5.0 units per cc. In view of the wide range of sensitivity, the average amount of penicillin used in treating this organism must, of necessity, be greater than with the more susceptible bacteria. We have observed three cases in which this organism developed increased resistance to penicillin during therapy. However, upon utilizing a larger dose of P.O.B., the infection was controlled. For the type of cases shown in Table III, a single daily dose of 300,000 units of P.O.B. is sufficient. For patients acutely ill with staphylococcal infection or with bacteremia, it is strongly advised that 300,000 units to 1.2 million units be given at twelve-hour intervals. For staphylococcal meningitis, the same dosage should be given plus intrathecal administration of penicillin in aqueous solution. For staphylococcal infections in which the organism is in the more resistant range (1 to 5 units per cc.), it is advisable to use penicillin in aqueous solution in doses of 10 to 20 million units or more daily. We have used this procedure due to the fact that when P.O.B. is given in doses of 1.2 million units, the volume of the mixture is such that there is a limit to the number of injections that can be given intramuscularly.

STREPTOCOCCAL INFECTIONS

The treatment schedule and description of the thirty-one study cases of streptococcal infections are shown in Table IV. Eight of these cases were pharyngitis and tonsillitis due to beta hemolytic streptococci. The response in these cases was excellent with only one patient requiring more than four injections. This case was one of particularly severe follicular tonsillitis. In all cases there was rapid improvement in subjective symptoms within twenty-four hours. All cases were cultured repeatedly for the beta streptococci. By the time treatment was completed and for at least five days subsequently, cultures were negative for this organism. A recent report[8] has shown that

TABLE IV

STREPTOCOCCAL INFECTIONS—31 CASES

TREATED BY A SINGLE DAILY INTRAMUSCULAR INJECTION OF CALCIUM PENICILLIN IN BEESWAX AND PEANUT OIL

No. Single Daily Doses Penicillin	Total Cases	Sex		Range of Single Daily Dose Penicillin (x 1000)	Range of Total Units (x 1000)	Remarks
		M	F			
Pharyngitis and Tonsillitis—8 Cases (Beta Hemolytic Strep)						
1	3	3 A		300	300	Results satisfactory in all cases unless otherwise stated.
2	1		1 A	300	600	
3	2	1 A	1 C (T)*	100–300	300–900	
4	1		1 C (T)*	100	400	* Severe tonsillitis.
8	1		1 A (T)*	300	2,400	
Erysipelas—4 Cases						
3	1	1 I		100	300	† Comparable case treated simultaneously with sulfadiazine. Result more rapid with penicillin.
4	1	1 C		90	360	
5	1		1 A	3–150, 2–100	650	
9	1	1 A†		300	2,700	
Cellulitis—17 Cases						
1	1	1 A		300	300	
2	2	2 A		100–300	200–600	
3	4	2 A	2 A	150–300	450–900	
4	7	3 C, 2 A	2 A	90–300	360–1,200	
5	1	1 A		300	1,500	
7	1	1 A		300	2,100	
9	1		1 A	300	2,700	
Mastitis—2 Cases						
5	1		1 A	300	1,500	Excellent response, resolved within period of treatment.
8	1		1 A	300	2,400	

T—Tonsillitis. I—Infants to 1 year. A—Adults above 16 years. C—Children 1 to 16 years.

Standard material for single 24 hour dose, 300,000 units calcium penicillin in 4.8% beeswax and peanut oil contained in 1 cc—other doses noted in table represent mixture used in process of development of the standard material.

Preferred plan of therapy: Single daily dose—3,000 units per lb. up to 100 lbs. 300,000 units 100–200 lbs. 600,000 units above 200 lbs.

50 per cent of a group of beta hemolytic streptococcus carriers had the organism eliminated from the pharynx by single daily injections of P.O.B. for five to eight days.

Four patients with erysipelas treated as shown in Table IV responded excellently. One severely ill adult required nine single daily injections of 300,000 units of P.O.B. with the lesion regressing within four to eight days. A comparable case was treated with sulfadiazine but the response of the patient treated with penicillin was more rapid.

Seventeen patients with cellulitis responded to treatment as shown in Table IV.

Within twenty-four hours a definite subjective improvement occurred with the lesions beginning to subside.

Two patients with mastitis treated for five and eight days, respectively, with single daily injections of 300,000 units of P.O.B. responded dramatically.

The average *in vitro* susceptibility of ninety-eight strains of beta hemolytic streptococci to penicillin (primarily G) was 0.02 Oxford units per cc. The range of susceptibility and the clinical response indicate that a single daily dose of 300,000 units of P.O.B. is adequate in all but the overwhelming bacteremias, in which this or larger doses given at twelve-hour intervals should suffice. For beta hemolytic streptococcal meningitis, a single daily dose of 300,000 units plus the usual intrathecal administration of penicillin in aqueous solution should suffice.

TABLE V

IMPETIGO—38 CASES

TREATED BY A SINGLE DAILY INTRAMUSCULAR INJECTION OF CALCIUM PENICILLIN IN BEESWAX AND PEANUT OIL

No. Single Daily Doses Penicillin	Total Cases	Sex		Range of Single Daily Dose Penicillin (x 1000)	Range of Total Units (x 1000)	Remarks
		M	F			
1	1	1 I		20	20	Results satisfactory in all cases unless otherwise stated.
1	2	2 I		75	75	
1	1	1 C		90	90	
1	3		3 C	150	150	Excellent response to penicillin. Within 24 to 48 hours lesions dried with cigarette paper appearance.
1	1	1 A		300	300	
2	1	1 I		20	40	
2	1	1 C		40	80	
2	2	2 C		75	150	
2	2	2 C		90	180	
2	1	1 C		1–40, 1–50	90	
2	2	2 I		100	200	*Recurrence in few days. Responded well subsequently to 4 doses of 100,000 units.
2	1	1 C*		100	200	
2	1	1 C		150	300	
3	2	2 C		90	270	
3	4	4 A		150	450	
3	1		1 A	200	600	
4	1	1 C		100	400	
4	2	1 I, I C		150	600	
4	2	2 A		2–200, 2–150	700	
4	1	1 A		200	800	
4	1	1 A		300	1,200	
5	3	2 C	1 C	50	450	
5	1	1 C		90	250	
6	1	1 C		150	900	

I—Infants to 1 year. A—Adults above 16 yrs. C—Children 1 to 16 yrs.

Standard material for single 24 hour dose, 300,000 units calcium penicillin in 4.8% beeswax and peanut oil contained in 1 cc—other doses noted in table represent mixture used in process of development of the standard material.

Preferred plan of therapy: Single daily dose—3,000 units per lb. up to 100 lbs. 300,000 units 100–200 lbs. 600,000 units above 200 lbs.

Alpha hemolytic streptococcus viridans, non-hemolytic streptococcus and streptococcus faecalis will be discussed subsequently.

IMPETIGO

Table v shows the schedule of therapy in the study group of thirty-eight patients with impetigo who were also treated by single daily injections of P.O.B. The response of impetigo to this treatment was particularly striking in that within twenty-four to forty-eight hours the lesions became dry with a cigarette paper appearance. No local medication was given and it seems advisable that the crusts should not be removed when parenteral administration is utilized. Thirty-three of the thirty-eight patients responded to single injections of the P.O.B. given over one to four days.

SUBACUTE BACTERIAL ENDOCARDITIS

The status of subacute bacterial endocarditis has been well reviewed.[9] However, none of the patients in the cases described had received P.O.B.

Six patients with subacute bacterial endocarditis have been treated with P.O.B. and a detailed report will be published shortly. However, the essential points in these cases are as follows: Of the first three who obtained satisfactory results, two have been followed for one year and one for three months. The first two cases had non-hemolytic streptococci sensitive *in vitro* to 0.1 to 0.2 Oxford units per cc., respectively. The third case had an alpha hemolytic streptococcus viridans sensitive *in vitro* to 0.05 Oxford units per cc. These patients responded satisfactorily when 300,000 units of P.O.B. was given at twelve-hour intervals for approximately thirty days. A fourth patient with an alpha hemolytic streptococcus viridans sensitive *in vitro* to 0.04 to 0.05 Oxford units per cc. was treated by a single injection of 300,000 units of P.O.B. for about thirty days and became bacteriologically negative. However, ten days after therapy was concluded, she expired following rupture of an aortic cusp. The patient in a fifth case, also due to alpha hemolytic streptococcus viridans sensitive *in vitro* to 0.05 Oxford units per cc., was treated with 300,000 units of P.O.B. at twelve-hour intervals. This patient had negative blood cultures after the second week of therapy. He subsequently expired in the fifth week of treatment due to rupture of a cerebral vessel which was proved to have a mycotic aneurysm at the point of rupture.

The sixth patient, a most interesting one, proved to have a Streptococcus faecalis resistant *in vitro* to approximately 10 to 20 Oxford units of penicillin per cc. The doses of P.O.B. were increased until as much as 1.2 million units was given at six-hour intervals and blood levels of 10 to 20 units per cc. were obtained. However, as mentioned previously, in view of the large volume of the mixture which must be injected, the P.O.B. had to be discontinued. It is this type of case, in which tremendous quantities of penicillin are necessary, that penicillin in aqueous solution is desirable. Subsequently, this patient was given 20 to 24 million units of penicillin by constant intravenous drip for thirty-three days. Blood levels ranging from 40 to 80 Oxford units per cc. were maintained. For the last three weeks of therapy, the patient's blood cultures were negative and at the time of this writing the patient has continued to be negative for an additional two weeks. This latter case emphasizes the necessity for determining the *in vitro* susceptibility (also in the patient's pre-treatment serum) of the organism cultured from cases of subacute bacterial endocarditis. In addition, it is important to maintain continuously a blood level which is several times the susceptibility of the organism, for at least a month. This case also emphasizes the fact that the lack of toxicity of penicillin places practically no limit on the amount which

can be given in those cases in which it is indicated.

The average range of *in vitro* sensitivity of forty-six strains of alpha hemolytic streptococci was 0.04 to 0.1 Oxford units per cc. For thirty-one strains of non-hemolytic streptococci it was 0.1 to 0.4 and for sixteen strains of Streptococcus faecalis, 3.0 to 20 Oxford units per cc.

SYPHILIS

Seventy-five patients with early syphilis have been treated by a single daily injection of 300,000 units of P.O.B. for eight days for a total of 2.4 million units. The details in these cases are in press.[10] Fifteen cases could not be followed other than during the initial period of therapy. Fifty-eight of the sixty cases observed for three to eighteen months gave satisfactory results. Forty of these fifty-eight cases have already attained seronegativity. An additional eighteen patients showed satisfactory progress at the time of the last serological examination. Two patients with secondary syphilis are classified as failures.

In view of the fact that failures have been encountered on this schedule, whether P.O.B. or penicillin in aqueous solution is given, a new group has been started which has been given the same daily dose of 300,000 units of P.O.B. over a period of sixteen days for a total of 4.8 million units.

An additional group of patients with early syphilis is being treated on the same schedule with 300,000 units of crystalline potassium penicillin G in 4.8 per cent beeswax in peanut oil contained in 1 cc. The early results with the crystalline potassium G, P.O.B. are as satisfactory as with amorphous penicillin. This is shown by the satisfactory spirochete disappearance time and rapid healing of primary and secondary lesions. Further data on crystalline potassium penicillin G in beeswax and peanut oil will be brought out subsequently in this paper.

MISCELLANEOUS GROUP

Fifty-eight cases are shown in Table VI. The first group is composed of ten cases of Vincent's angina treated as shown with excellent response. Rapid subjective and objective improvement occurred within twenty-four to forty-eight hours. Parenteral therapy seems particularly necessary in those cases with deep-seated lesions. The usual supportive type of treatment for this condition is also essential.

Thirty-eight of forty-one cases of acute sinusitis, also shown in Table VI, responded well to single daily injections of P.O.B. A total of three to six injections is usually necessary. The chronic cases had an equivocal or unfavorable response even though single daily injections were given for as long as seven or eight days. It is essential that adequate drainage be maintained during penicillin therapy.

The acute symptoms in four cases of acute tracheitis and three cases of acute bronchitis responded well within the period of therapy as shown in Table VI.

Two patients with actinomycosis have responded very well to P.O.B. One was a long-standing infection on the dorsum of the neck, the other a pulmonary lesion. Both of these patients responded to 300,000 units of P.O.B. at twelve-hour intervals for thirty days. As of the present, six months following therapy, there is still no evidence of relapse.

An additional patient, a white male, aged twenty, with actinomycosis of the anterior chest wall becoming apparent late in February, 1946, is under therapy at the present time. Subsequent to the initiation of the disease he proceeded to have a marked febrile course with profuse drainage after incision of the lesion. In June, 1946, he developed an abscess of the prostate gland which was incised and drained through a perineal approach. Penicillin therapy in moderate quantities had been instituted

TABLE VI

MISCELLANEOUS GROUP—58 CASES

TREATED BY A SINGLE DAILY INTRAMUSCULAR INJECTION OF CALCIUM PENICILLIN IN BEESWAX AND PEANUT OIL

No. Single Daily Doses Penicillin	Total Cases	Sex		Range of Single Daily Dose Penicillin (x 1000)	Range of Total Units (x 1000)	Remarks
		M	F			
Vincent's Angina—10 Cases						
1	2	1 A	1 A	200–300	200–300	Result satisfactory in all cases unless otherwise stated.
2	1		1 A	300	600	
3	2	1 A	1 A	150–300	450–900	Excellent response to penicillin with rapid subjective improvement within 24 to 48 hours.
4	2		2 A	300	1,200	
		1 C, 1 A	1 A	150–300	750–1,500	
Sinusitis—41 Cases						
1	2	1 A	1 A	100–300	100–300	* Chronic cases, response equivocal; acute or acute exacerbation of sinusitis responds to penicillin—cases noted were acute.
2	5	3 A	2 A	150–300	300–600	
3	14	11 A	3 A	100–300	300–900	
4	7	6 A	1 A	300–300 plus 3–150	1,200–1,650	
5	7	4 A, 1 C	2 A	80–300	400–1,500	
6	3	1 A, 1 C	1 A	200–300	1,200–1,800	
7	2		2 A*	300	2,100	
8	1		1 A*	300	2,400	
Tracheitis—4 Cases						
2	1		1 A	300	600	
3	2	2 A		300	900	
4	1	1 A		300	1,200	
Acute Bronchitis—3 Cases						
1	1	1 A		300	300	
2	2	1 A, 1 C		90–300	180–600	

I—Infants to 1 year. A—Adults above 16 years. C—Children 1–16 years.

Standard material for single 24 hour dose, 300,000 units calcium penicillin in 4.8% beeswax and peanut oil contained in 1 cc—other doses noted in table represent mixture used in process of development of the standard material.

Preferred plan of therapy: Single daily dose—3,000 units per lb. up to 100 lbs. 300,000 units 100–200 lbs. 600,000 units above 200 lbs.

without any particular modification in the course of his disease. When he was admitted to Walter Reed General Hospital, he was placed on 300,000 units of P.O.B. at twelve-hour intervals with 1 million units of penicillin in aqueous solution given as booster doses at the sixth and eighteenth hour. In July, 1946, the *in vitro* test of his organism showed it to be resistant to 10 to 20 units of penicillin per cc. As mentioned in the foregoing data, when extremely high blood levels of penicillin are required it is advisable to give penicillin in aqueous solution. He was, therefore, placed on 20 million units of penicillin in aqueous solution daily by the constant intravenous drip method.

His blood level was approximately 20 to 40 units per cc. By the third week subjective improvement occurred, there was decrease in fever and considerably less drainage. At that time he was placed on 40 million units of penicillin in aqueous solution daily by constant intravenous drip and, as of the present writing, a short time after initiation of this dose his temperature has subsided to normal. The blood level following this dose was 40 to 80 Oxford units per cc. It is hoped that subsequently further information on this case can be reported.

Sixteen patients* with urinary tract infection due to Streptococcus faecalis have been treated and made bacteriologically negative in the following manner with P.O.B. Moderate dehydration has been initiated approximately twelve to twenty-four hours prior to treatment and continued during the course of therapy. Three hundred to six hundred thousand units of P.O.B. were given for six to eight days at intervals of twelve hours. The patients were all advised to retain their urine as long as possible. By this means penicillin levels in the urine of 1,000 or more units per cc. have been maintained constantly during the period of treatment.

The routine in this hospital for preoperative cases of bronchiectasis has been as follows: Three hundred thousand units of P.O.B. once daily until the sputum output is minimal. Postoperatively, these patients received 300,000 units of P.O.B. at twelve-hour intervals for approximately seven days. The therapeutic and protective value of penicillin in over fifty patients treated in this manner appears to be well established.

Of the 4,000 patients who have received routine daily treatment with P.O.B., many have been from the amputation and orthopedic services. These patients have received daily doses of P.O.B., usually 300,000 units, pre- and postoperatively. Although evaluation is difficult, there appears to be little doubt of the protective value of penicillin in these cases.

Other types of cases in which the patients have received pre- and postoperative P.O.B. have been those who have had tonsillectomy, adenoidectomy and dental extractions. The usual dose has been 300,000 units twenty-four hours prior to operation and the same dose for approximately three to five days following surgery. This procedure has been used particularly in patients with rheumatic heart disease.

In terms of consecutive daily intramuscular injections of calcium penicillin in beeswax and peanut oil, patients have tolerated well as many as 180 doses of this mixture.

COMMENT

In this period of study of 600 patients and routine therapy of approximately 4,000 patients receiving 60,000 injections, assays of the blood for penicillin at four-hour intervals for twenty-four hours or at the twenty-fourth hour have been made in approximately 10,000 instances. In addition, approximately 4,000 penicillin assays of the urine have been accomplished. As previously reported,[4] following a single injection of 300,000 units of calcium penicillin in 4.8 per cent beeswax (by wt.) in peanut oil contained in 1 cc., assayable blood levels will persist for approximately twenty-four hours in 70 to 75 per cent of the cases. In the remaining instances, assayable levels will be present for sixteen to twenty-four hours. The aforementioned statement has been corroborated by the numerous blood level determinations mentioned above. The present standard preparations of amorphous calcium penicillin in beeswax and peanut oil present no difficulty in administration since they can be administered with a 22-gauge needle at room temperature (25°c.), if necessary. However, the practical needle

* This study was done with Lt. Col. Lloyd G. Lewis, chief of the Genito-Urinary Section.

for routine use is the 20-gauge. In the early preparations some difficulty in withdrawal and administration was experienced. As a rule, this was due to the occasional difficulty in properly blending the penicillin powder with the result that the mixture was quite viscous and occasionally large particles obstructed the passage of the mixture through the needle. The method of administration has been reported previously.[4] However, in brief, the vial containing the mixture should be kept for three to five minutes under the hot water tap at 56° to 60°C. The preparation is shaken at intervals so that there is thorough warming of all the material. At this time the mixture may be withdrawn with an 18-gauge or larger needle into a Luer-Lock syringe and should be allowed to cool to room temperature prior to injection. It is *definitely unnecessary* to *re-warm* the syringe. For the intramuscular injection a 20-gauge needle should be utilized. The P.O.B. should not be forced into the 20-gauge needle until the needle has been inserted in the muscle, since the mixture occasionally hardens in the metal needle, making it difficult to inject. A *dry* syringe and needle should *always* be used Injections may be given in the upper quadrant of the buttock or in the deltoid, anterior thigh or triceps muscles. At the present time, disposable cartridges containing 300,000 units in 1 cc. of the standard formula are available. These facilitate the administration of this mixture.

It has been stated previously[1,2,3,4] that due to the hygroscopic factor in the amorphous sodium salt of penicillin, the amorphous calcium salt must be used in the preparation of penicillin in beeswax and peanut oil mixtures. This is contrary to a recent report[11] stating that the sodium salt may be used as well as the calcium. We have observed that the amorphous sodium salt not only produces erratic and less prolonged levels than the calcium, but more important, the amorphous salt does not maintain its stability.[1,2,3,12] Furthermore, there is a tendency for the particles of amorphous sodium salt to congeal into clumps in the beeswax and peanut oil mixture preventing passage of the material through the needle.

In recent months we have found that when 300,000 units of crystalline calcium or sodium penicillin G is suspended in 4.8 per cent beeswax in peanut oil contained in 1 cc. the resulting mixture is rather liquid and does not produce assayable levels for more than twelve to fourteen hours after a single injection. Fortunately, if the potassium salt is substituted for the above, 300,000 units of crystalline potassium penicillin G in 4.8 per cent beeswax (by wt.) in peanut oil contained in 1 cc. will produce a mixture comparable to the present standard amorphous calcium P.O.B.

Over 100 patients with varying conditions have received single daily doses of crystalline potassium penicillin G in beeswax and peanut oil and have had numerous blood and urine levels of penicillin determined. Not only have the clinical results in these patients been as satisfactory as with amorphous calcium P.O.B., but 85 per cent of the cases have had assayable levels for approximately twenty-four hours after a single injection of this crystalline potassium G, P.O.B. The remaining patients have had assayable levels of penicillin for sixteen to twenty-four hours. The potassium crystalline P.O.B. shows no deterioration even at temperatures of 100°C. for twenty-four hours.

In our hands it has not been possible to prolong the action of penicillin by the use of water in oil emulsions. Intramuscular doses of 100,000, 200,000 and 300,000 units of penicillin made up in water and oil emulsions have only yielded blood levels comparable to those produced by the same doses in aqueous solution.

Twenty-four hours after the intramuscular injection of P.O.B., there was some soreness to pressure at the site. This was usually gone by the forty-eighth to the seventy-second hour. This sequence of events occurred after each injection although administered at a different site. The soreness was no more severe than that following the multiple injections of aqueous penicillin. Patients had the added advantage of receiving only one injection a day, and in addition, many could be treated on an ambulatory basis. In infants and children, a nodule may be palpable for quite some time after an injection of P.O.B., but usually this is due to the material having been given subcutaneously instead of intramuscularly. It is not desirable to massage the site of injection since diffusion of the material will accelerate absorption and increase local soreness.

In this series of approximately 4,000 cases receiving 60,000 injections, only two instances of sterile foreign body abscess have occurred. Both of these happened when the material was given subcutaneously and corroborates the observations[1,2] which have been noted in tissues of animals and humans that a much greater inflammatory reaction occurs when the mixture is given subcutaneously. Clinically, this is also true as indicated by subjective and objective findings. This has also been corroborated by others[13] but is contrary to a recent report,[14] the authors of which state that on the basis of clinical observation less discomfort occurs following the subcutaneous administration of P.O.B.

Hamsters and rabbits which had been injected intramuscularly with P.O.B. were followed for six and three months, respectively. Tissues were also observed from humans who had expired from various causes one to two months after receiving numerous intramuscular injections of P.O.B. Upon microscopic examination twenty-four hours after the intramuscular injection of P.O.B., the particles of beeswax are separated by collections of polymorphonuclear cells, large mononuclear cells and foreign body giant cells. No muscle necrosis is associated with this reaction, the fibers merely being separated. Beeswax is removed from the tissues by phagocytes and is usually gone by the tenth to the thirtieth day. Very little fibroblastic reaction occurs and that disappears within several months. In tissue from humans at the time mentioned above, numerous serial sections of the muscle were necessary in order to find the site of injection and beeswax was not identified. At this time a few minute cysts, some partially collapsed, having thin fibrous walls with scattered giant cells were present. The same picture was present in the hamsters and rabbits. These minute cysts are no different from those found after the intramuscular injection of any medication in an oil. The absorption of beeswax has also been reported by others.[15,16,17]

Up to the present time, as far as we have been able to ascertain in the treatment of approximately 4,000 patients, there has been no evidence of paraffinomas developing.

The incidence of allergic reactions in this large group of patients who have received P.O.B. has been about 5 per cent. These reactions have varied from slight urticaria to a generalized type and angioneurotic edema. They are similar to those which have occurred with other types of penicillin and methods of administration. The peak of the reaction is usually attained by the fourth day after initiation and gradual subsidence then occurs with complete relief by the twelfth day. We have observed two patients who continued to have mild urticaria for approximately a month after treatment was initiated.

An id type of reaction which has been reported by others[18] has occurred in six patients who had a history of epidermo-

phytosis. This reaction involved the axilla, groin and palm of the hands and the height of the reaction tended to occur approximately twelve hours after each injection of P.O.B. and subsided by the twenty-fourth hour just prior to the next injection. In none of these cases was it necessary to stop the drug.

Local reactions at the site of injection occur occasionally, but are definitely more frequent when the P.O.B. is given subcutaneously. These seem to be of an allergic character since relief occurs when cold applications are made or anti-allergic therapy is instituted. However, they tend to be markedly aggravated by the use of hot applications.

Benadryl (beta-dimethylaminoethyl benzhydryl ether hydrochloride), a new drug, has been effective in most instances in alleviating the allergic manifestations produced by penicillin. The usual dose of benadryl has been 50 mg., three to six times daily. The two reactions mentioned above, in which the patients persisted in having urticaria for about a month, were finally controlled by the administration of 50 mg. of benadryl three times a day. Twenty-four patients who manifested allergic reactions to penicillin were successfully continued on treatment with P.O.B. when benadryl was given simultaneously. No other untoward reactions have been noted as a result of the administration of P.O.B.

Seventy-five patients* were given skin and patch tests with all constituents of the P.O.B. before and after treatment with the mixture.† Only one individual showed any degree of sensitivity, and this was to penicillin. In addition, in a recent report[19] it was stated that beeswax combined with peanut oil, because of its non-antigenic character, should be an ideal medium for delaying the absorption of penicillin.

In a previous report,[4] it was stated that no loss of potency of the P.O.B. had occurred at 10°, 25° and 37°C. for nine months. At the time of this writing, over 200 different batches of P.O.B., which have been maintained at 10°, 25° and 37°C. for varying intervals of time up to two years, have been tested frequently for loss of potency. No deterioration of the penicillin has occurred at 10° and 25°C. in those batches which have been maintained at these temperatures for twelve to eighteen months. The majority of those at 37°C. maintained their potency for about nine months and subsequently there has been a gradual loss. These results indicate that it is unnecessary for P.O.B. to be refrigerated and that full potency will be maintained at 25°C. (room temperature) for at least one year. Complete details on the stability studies will be published shortly.

SUMMARY

1. Study of 600 cases plus clinical observations of 4,000 cases given 60,000 intramuscular injections of calcium penicillin in beeswax and peanut oil at twenty-four or twelve-hour intervals, gave results as satisfactory as those obtained by the multiple injections of penicillin in aqueous solution.

2. The incidence of allergic reactions after intramuscular injection of calcium penicillin in beeswax and peanut oil is approximately 5 per cent.

3. Calcium penicillin in beeswax and peanut oil has shown no loss of potency at 10°C. and 25°C. (room temperature) for at least one year. At 37°C. potency has been maintained for about nine months.

* This study was done with Lt. Col. Louis E. Lieder, Chief of the Allergy Section.

† It is very important that all patients receiving penicillin be questioned as to any history of allergy.

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Combined Staff Clinics

Hypoglycemia

These are stenotyped reports of combined staff clinics of the College of Physicians and Surgeons, Columbia University. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Frederick K. Heath.

DR. HENRY ARANOW, JR.: The subject this morning was chosen primarily because it offers a topic for discussion of certain physiological mechanisms and their rather direct connection with therapeutic management and pathological sequelae.

Hypoglycemia is defined as a lowered content of glucose in the blood. An important qualification which should be made is that the absolute value of the blood sugar, as measured in mg. per cent, may not have as much significance in the individual patient as its value in relation to his usual blood sugar and the rate with which it falls.

There have been recent developments in carbohydrate metabolism which are of great importance, and it is the purpose of this clinic primarily to try to integrate this newer knowledge with the clinical problems involved. I have asked Dr. Stetten to review briefly for us some of the latest concepts in carbohydrate metabolism.

DR. DEWITT STETTEN, JR.: After discussing this problem with Dr. Aranow, I concluded that it would be well to review for you material to which you have already been exposed, namely, the sources of blood glucose and the dispositions which the body makes of glucose both normally and abnormally. The accompanying chart (Fig. 1) is intended to represent the reactions that are pertinent to this discussion and suffers from the inherent defects of such diagrams in that much has been omitted.

The blood glucose may be pictured as arising from three types of processes. The first of these is the absorption of glucose across the intestinal mucosa. Glucose as such is, of course, a trivial dietary ingredient but large amounts of glucose arise in the intestinal tract as a result of digestion of dietary polysaccharides. Of the polysaccharides of the diet, cellulose in man is not appreciably digested, but starch and glycogen, as well as the common disaccharides, are broken down by the action of the several saccharolytic enzymes, among which are included salivary ptyalin and pancreatic amylase. The monosaccharides which escape bacterial fermentation are absorbed through the portal circulation and delivered to the liver.

A second source of body glucose, termed glycogenolysis, is from the breakdown of glycogen in the liver. For reasons which will be discussed later, the glycogen of muscle does not contribute directly to this process. The intimate mechanism of the glycogenolytic process has been clarified by the work of the Coris, of St. Louis, who have shown that the initial process is one of phosphorolysis, rupture of glucosidic bonds between hexose fragments of glycogen by the introduction of phosphoric acid. The reaction product, glucose-1-phosphate, is readily transformed in the body to glucose-6-phosphate, and these two reactions apparently occur wherever one finds glycogen. The next necessary reaction, if this product is to be converted into glucose, is not so wide-spread. This reaction, which may be written:

$$\text{Glucose-6-phosphate} \xrightarrow{\textit{phosphatase}} \text{glucose} + \text{inorganic phosphate}$$

is, in the mammal, more or less peculiar to the liver, although it undoubtedly can occur in other tissues. At all events, this last step does not occur in muscle, and it is because of this lack of the necessary phosphatase in muscle that muscle glycogen is not available as a direct source of blood glucose.

A third source of blood glucose, which has been called gluconeogenesis, proceeds from non-carbohydrate precursors. Among these are the glucogenic amino acids, glycerol, and possibly fatty acids. In addition I should like to include fragments which have resulted from the breakdown of glucose itself and which may subsequently be reconstituted into glucose.

Each of these three types of processes may be disturbed, and such disturbances may in turn result in a lowering of the level of blood glucose. In the first place, the absorption of glucose from the lumen of the gastrointestinal tract may be reduced, most obviously in starvation. Perhaps of greater clinical interest is the interference with this same process seen in sprue. In this disease the failure of the blood glucose to rise after oral administration of glucose has been attributed to faulty absorption.

We have diseases in which, for one reason or another, liver glycogen fails to serve as a source of glucose. Such failure might be anticipated when after a fast the liver glycogen is depleted. The most interesting example, however, is the situation in von Gierke's disease, which Dr. Mason will discuss later in this conference. It may be suspected that in von Gierke's disease one of the systems which is deficient is the liver phosphatase. (Fig. 1.) Failure of this enzyme to operate normally would necessarily bring about an impairment in the conversion of liver glycogen into glucose.

A third type of situation in which one of the normal sources of blood glucose is interrupted occurs perhaps in Addison's disease. It is the belief of many that the more oxygenated adrenocortical steroids, those with four and especially five oxygen atoms, contribute in some as yet very unclear way to the conversion of glucogenic amino acids into glucose. While the exact nature of this participation is quite mysterious, the evidence upon which it is based, the rise in blood glucose concentration, the increase in liver glycogen, the increased urinary nitrogen observed after administration of these agents, is very suggestive. It may be inferred, therefore, that the hypoglycemia of hypoadrenalism is perhaps contributed to by an interference with the gluconeogenic source of glucose.

Glucose is thus seen to arise in the animal by absorption and by synthesis more or less continuously, and in the normal animal disposition must be made of all this glucose. Although glucose is generally pictured as a very reactive substance, the fact is that, in the body, there are very few reactions in which it is certain that glucose enters. Of these, far and away the most important seems to be its phosphorylation, and in general it may be stated that if glucose is to be utilized in the body, it probably must first be phosphorylated. The reaction involved may be written:

$$\text{Glucose} + \text{adenosine triphosphate} \xrightarrow{\textit{hexokinase}} \text{glucose-6-phosphate} + \text{adenosine diphosphate}$$

Phosphorylation, which very likely occurs at the cell membrane, may be regarded as a more or less obligatory first step in glucose utilization, and the product, glucose-6-phosphate, as indeed is true of the other phosphorylated intermediates, is predominantly an intracellular constituent. Once formed, glucose-6-phosphate is exposed to many possible fates. In the liver (but not in the muscle), it may be hydrolyzed by

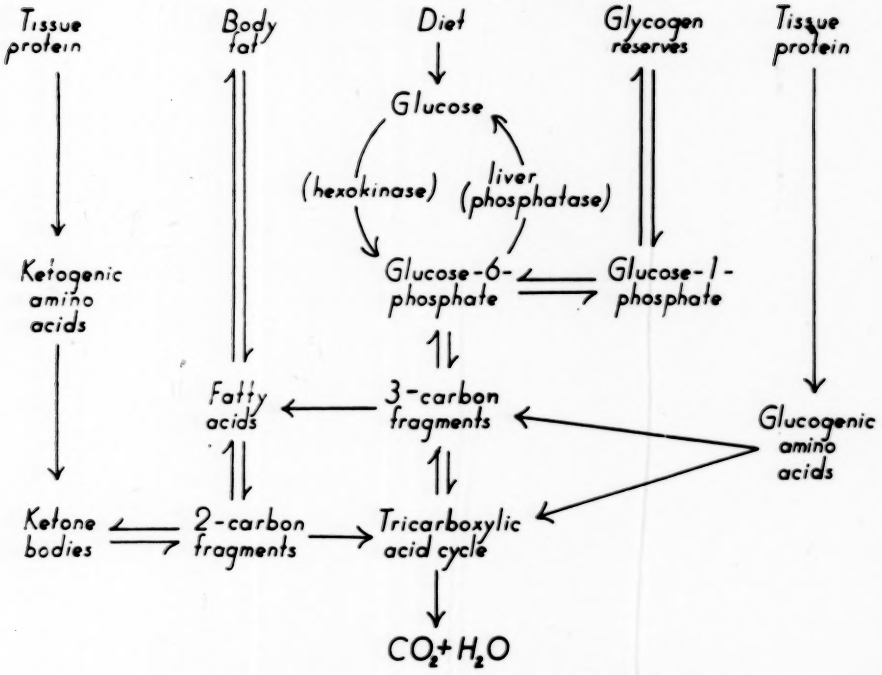

FIG. 1. *Diagram showing origins and fates of body glucose.*

the action of the appropriate phosphatase to regenerate glucose. It may, by reversal of the previously described reactions, be transformed into glycogen. Most important perhaps is its further breakdown, which is indicated in but fragmentary fashion in Figure 1, but which you will recall as the Embden-Meyerhof cycle, followed by the Krebs tricarboxylic acid cycle, giving rise ultimately to CO_2 and H_2O.

Other things may happen along the line. For instance, we know that relatively large amounts of glucose are converted each day into fatty acid in the animal, a process pictured in the diagram as stemming from the 3-carbon fragments that arise from glucose.

It would be interesting to have at hand information concerning the relative amounts of glucose arising from the several sources mentioned and utilized in the several processes, per day, in the normal man. Unfortunately, such information is lacking. I can, however, give you analogous information derived from the rat, which may or may not be similar to the situation in the human. In our rats, which ate between 12 and 15 Gm. of glucose each day, the contribution made to body glucose by the breakdown of glycogen was only about ½ Gm. Approximately 3 per cent as much glucose came from glycogen as came from the diet. The contribution made by synthesis from smaller fragments amounted to about 5 Gm. per day, which is about 30 per cent as much as was consumed in the diet.

These were normal rats and they utilized every bit of sugar that they ate and every bit that they made, and we have been interested, therefore, in learning how much of the sugar went to each of the several products. Of the sugar that was utilized by these animals, only about 3 per cent was converted to glycogen, and a great deal more, some 30 per cent, went to form fatty acids. The remainder presumably was metabolized to CO_2 and to other products not included in the present scheme.

I have previously indicated how failure in one or another of the sources of supply of glucose may result in a fall in the concentration of glucose in the blood. Clearly, a

fall in blood glucose may also result from exaggeration of the processes of utilization and all of these processes must in large part be dependent upon one reaction (the only reaction which the several pathways of utilization share in common), the hexokinase reaction. If this reaction is proceeding normally, one would expect to find normal amounts of glucose converted to CO_2, to glycogen and to fatty acids each day. If this reaction is inhibited, one would predict a retardation in all the various modes of utilization of glucose, and it would appear at the present time that this is the situation in the diabetic individual. If, on the other hand, the hexokinase reaction is pictured as proceeding at an excessively rapid rate, the several pathways of glucose utilization would be accelerated and hypoglycemia would result.

Hexokinase is a very widely distributed enzyme and it catalyzes one of the very fundamental reactions of all living tissues. The samples of hexokinase which have been studied by the Coris and their collaborators have been found, if they arise from animal sources, to be subject to a specific inhibition and the inhibitor which has been studied can be isolated from the anterior pituitary gland. The corollary which follows, I think, is that in the normal animal there is a physiological and continuous inhibition of the hexokinase reaction.

The Coris have also demonstrated that this inhibition may be strikingly prolonged by the addition of certain preparations of oxygenated adrenocortical steroids. Perhaps their most impressive discovery is their demonstration that the inhibition of the hexokinase reaction is completely obliterated by the addition of insulin.

The importance of these findings is tremendous. In the first place, I believe that this is the first time in the history of biochemistry that a hormone has been caused to operate in a reasonable fashion in a test tube, and in this study, not one but three hormones have been caused so to behave. In the second place a satisfactory position may now be assigned to insulin in its rate-determining rôle in carbohydrate metabolism.

The activity of hexokinase in the body may be pictured as subject to influence by several groups of hormones. Lack of anterior pituitary inhibitor, the presence of an excess of insulin which obliterates the physiological inhibition, or the lack of certain adrenocortical substances, which perhaps normally prolong the inhibition—any of these three will result in enhanced hexokinase activity. Glucose will be converted to glucose-6-phosphate at an excessive rate, more glucose will find its way to CO_2, to fatty acids and to glycogen, all demonstrated effects of insulin administration. From the point of view of the present clinic, the blood glucose level will fall.

I think it would be interesting if the many clinical categories of hypoglycemia which are to be discussed could be analyzed in terms of the process disturbed in each case, and I hope that Dr. Aranow will do that for us.

STUDENT: I should like to ask how and where adrenalin acts?

DR. STETTEN: The rôle of adrenalin in carbohydrate metabolism may be observed in two different forms, depending on the previous history of the animal. In the well nourished animal, the major effect of adrenalin is a prompt decrease in the stores of liver glycogen and an increase in blood glucose. In the previously fasted animal, on the other hand, this effect is excluded by the fact that there is virtually no liver glycogen present. What is seen under these circumstances is a decrease in muscle glycogen, a rise in blood lactate, and secondarily, a rise in liver glycogen. In both types of experiment, adrenalin seems to favor the conversion of glycogen to glucose-

6-phosphate. When this occurs predominantly in liver, a good part of the product is hydrolyzed to give glucose. In muscle, however, the necessary phosphatase for this reaction is lacking, and the major fate of the glucose-6-phosphate is degradation to lactate and other 3-carbon fragments. The liver of the previously fasted animal, depleted of glycogen, has a great tendency to deposit glycogen, and, under these circumstances, will use a portion of the lactate formed in muscle for glycogenesis.

As to the actual reaction affected by adrenalin, I should venture that it is either the conversion of glycogen to glucose-1-phosphate or the subsequent isomerization to glucose-6-phosphate.

A DOCTOR: What other enzymes are involved in the carbohydrate cycle?

DR. STETTEN: The enzymes involved in the several reactions of carbohydrate metabolism are too numerous to be included in the present clinic. Some of the more interesting ones are phosphorylase, which catalyzes the reversible conversion of glucose-1-phosphate into glycogen; phosphohexomutase, which operates on the interconversion of the 1- and the 6-phosphates of glucose; an isomerase, which aids in the establishment of the equilibrium between the phosphoric esters of glucose and fructose; phosphohexokinase, which introduces a second phosphate residue at the 1-position into fructose-6-phosphate; and zymohexase, which splits fructose-1, 6-diphosphate into the triose phosphates.

As will be seen, for practically each step (with few exceptions) an enzyme has either been demonstrated or postulated and it would seem futile at this time to continue the list. Thus far, few diseases have been related to specific disturbances in the action of these enzymes. An exception to this, worthy of note, concerns several of the enzyme systems which activate pyruvic acid and which employ as coenzyme, cocarboxylase. Cocarboxylase, as you know, is thiamine pyrophosphate, and the disturbance in pyruvic acid metabolism seen in thiamine deficiency is undoubtedly related to a disturbance in these enzymes.

TABLE I
HYPOGLYCEMIA*

I. Exogenous	1. Insulin overdosage	
II. Endogenous		
A. *Organic*	1. Hyperinsulinism	
		1. Pancreatic islet cell adenoma
		2. Pancreatic islet cell carcinoma
		3. Pancreatic islet cell hypertrophy
	2. Hepatic disease	
		1. Toxic hepatitis
		2. Fatty liver
		3. Diffuse carcinomatosis
		4. Von Gierke's disease
		5. Diffuse intrahepatic cholangitis
	3. Hypopituitarism	
		1. Destructive lesions
		2. Atrophy or infection
	4. Adrenal cortical insufficiency	
		1. Destructive granuloma
		2. Primary atrophy
		3. Destructive neoplasms
	5. Hypothyroidism	
	6. Thalamic lesions	
B. *Functional*	1. Increased insulin secretion (normal pancreas); autonomic imbalance	
	2. Decreased anterior pituitary or adrenal cortex secretion	
	3. Excessive oxidation; prolonged arduous exercise	
	4. Pregnancy and lactation	
	5. "Idiopathic postoperative" hypoglycemia	
	6. Alimentary hypoglycemia after stomach operations	

* Modified from CONN, J. W., *J. A. M. A.*, 115: 1669, 1940.

DR. ARANOW: I put on the board a list of the conditions which may be associated with hypoglycemia. (Table I.) Before discussing some of the more interesting mechanisms involved, I want to emphasize that by far the most common type is the first, i.e., a diabetic patient who has taken too much insulin for his metabolic needs during a particular period. It was Seale Harris's observation of such a case which led him to the realization that cases of spontaneous hyperinsulinism might exist.

Most of our knowledge of the physiological control of insulin secretion is both fragmentary and controversial. We know

that a fall in blood sugar leads to increased secretion of adrenalin and to stimulation of the sympathetic nerves, particularly the hepatic nerves. Where does this stimulation originate?

When the utilization of glucose is impaired, mobilization of depot fat is accelerated. This mobilization is probably mediated by the anterior pituitary, which may be acted upon by impulses from the adjoining brain. In 1924, Clark in England and Britton in this country provided evidence that the vagus nerve, particularly the right branch, apparently causes an increase in insulin secretion by stimulating the islets of Langerhans. That the vagus control of insulin secretion is not the major regulating mechanism, however, is shown by the fact that a fairly normal carbohydrate metabolism may be maintained by the completely denervated pancreas, and that vagotomy does not cause a detectable alteration in the glucose tolerance test.

LaBarre, in 1930, reported a complex, three-animal, crossed-circulation experiment which suggested that there was a center in the thalamic region which responds to hyperglycemia by decreasing insulin secretion, and vice versa. Keller has recently shown that hypothalamic lesions are the cause of occasional hypoglycemic crises, and that these crises cannot be prevented either by vagotomy or sympathectomy.

Now let us endeavor to make correlations between the chart which Dr. Stetten showed you (Table 1) and these clinical conditions. First, in insulin overdosage or overproduction we have an acceleration of the conversion of glucose to glucose-6-phosphate. This causes an increased "flow" along all of the lines, both the main lines and the side paths. We can see how an increased rate of conversion of glucose can result in lowered blood sugar unless more dietary glucose is constantly made available.

In man, the conversion of glycogen to glucose can occur only in the liver, and it is probable that most if not all of gluconeogenesis occurs there. In hepatic disease, therefore, hypoglycemia might be anticipated and does occur. It should be emphasized, however, that liver function must be very seriously deranged before this effect becomes manifest, since about 20 per cent of a normal liver is adequate to maintain resting carbohydrate function.

Ever since the discovery of insulin, the site and mode of its operation have been sought by experiment and anticipated in speculation. According to Cori's theory, in any form of hypopituitarism a very important inhibitor to the action of hexokinase is either diminished in amount or removed. Russell and others have shown that the oxidation of glucose is enormously increased in animals deprived of their anterior pituitary glands. Using evidence published by Lukens and Dohan, and Long and Lukens, Drury proposes that the fasting hypoglycemia seen in hypopituitarism may not be due primarily to impaired gluconeogenesis, as has been hitherto hypothesized, but may be due to increased utilization of glucose in the periphery, with a consequent reduction in the demand for gluconeogenesis. The brain, the obligate user of glucose, then has to suffer at times from this increased glucose oxidation by other tissues.

In adrenal cortical insufficiency, an analogous removal of inhibition may be assumed. When adrenalectomy is performed on animals with pancreatic diabetes, their diabetes is greatly ameliorated and gluconeogenesis, as estimated from nitrogen output, is reduced to normal levels. It is of interest that these animals, with normal gluconeogenesis, frequently show hypoglycemic reactions. According to Drury's hypothesis, these are due to better peripheral utilization of glucose, which thereby diminished the demand for gluconeogene-

sis. The more conventional explanation in both hypopituitarism and adrenal cortical insufficiency is that hypoglycemia is due to impaired gluconeogenesis.

In hypothyroidism marked slowing of glucose absorption may occur. The possibility exists that some of the cases which have been reported were "pituitary myxedema" rather than primary athyreosis.

The possible rôle of hypothalamic controls in the regulation of blood sugar levels has been mentioned.

The "functional" hypoglycemias present an important problem, since it is important to recognize them and to differentiate them from the "organic" group. Those in which "autonomic imbalance" or "functional hyperinsulinism" plays a rôle are usually characterized by a normal fasting blood sugar, with a tendency for the level of the blood sugar to fall to abnormally low levels from three to five hours after the ingestion of carbohydrates, particularly of readily absorbed carbohydrates. The tired people with mental and physical inertia due to hypoglycemia probably fall in this category, although at times their symptoms may be considerably more severe.

Hypoglycemia occurring in renal glycosuria, severe continuous muscular work, pernicious vomiting of pregnancy, cyclical vomiting in children, and in lactation is brought about by mechanisms which are practically self-explanatory.

A new group was added to the functional hypoglycemias by Dr. David W. Blood of our resident staff; in the February 23, 1946, issue of the *J. A. M. A.* he described three instances of postoperative hypoglycemia of great severity. The gravity and intractability of the hypoglycemic symptoms led to exploration of the pancreas in two cases but no organic cause for the lowered blood sugar was found. In none of the three instances was the original operation of a sort which might have been expected to have any direct effect on any of the organs concerned with carbohydrate metabolism.

The final group has been the subject of an exhaustive study by Ole K. Evensen, recently published in one of the Acta Medica Scandinavica supplements. In seventeen of thirty-seven patients who had had gastroenterostomies, and in thirty-eight of ninety-five patients with subtotal gastric resections he found abnormally low blood sugar values three or four hours after the ingestion of glucose. A very considerable proportion of these patients complained of symptoms referable to hypoglycemia several hours after normal meals. Evensen ascribed these phenomena to abnormally rapid emptying of the stomach, and has produced similar glucose tolerance curves by introducing glucose directly into the jejunum.

In discussing the symptomatology of hypoglycemia, a quotation from Dr. Seale Harris, who first described the syndrome of spontaneous hypoglycemia, seems appropriate: "The neurologic manifestations of hyperinsulinism are varied and fantastic. It may masquerade in the form of many functional nervous syndromes such as psychasthenia, neurasthenia, muscular asthenia, neurocirculatory asthenia, hysteria, migraine, petit mal, narcolepsy, epilepsy, and even the psychoses. Hyperinsulinism may also simulate some of the organic nervous diseases and has been mistaken for hemiplegia, paraplegia, encephalitis, neurosyphilis, and brain tumor."

With so extensive an array, it will not be profitable to review specific symptoms and signs in detail, but the stages of hypoglycemia (Wauchope) are worthy of note. In the first stage the symptoms are quite vague and the diagnosis is difficult. The patient feels weak and unwell, but in many instances this cannot be more precisely defined. A disinclination for bodily and mental exertion is noted. The second stage may be called that of adrenalin secretion, the body's attempt

to prevent further hypoglycemia by mobilizing glucose from liver glycogen. This is characterized by congestion or pallor of the face, sweating, palpitations, hunger, thirst, tremors and increased pulse pressure. In the psychic sphere, anxiety and disquiet are noted. In the third stage consciousness becomes affected; the mind is sluggish, speech inarticulate and movements uncoordinated. The fourth stage is signalized by convulsions, paralysis, and alterations of reflexes and the fifth stage by coma.

DR. ROBERT F. LOEB: I think it should be pointed out that not all patients with hypoglycemia progress through all five stages, though that is the most common sequence. In some patients, the onset of coma and convulsions is not preceded by any prodromal symptoms. Others have disturbances in behavior without hunger, sweating or other such indications of hypoglycemia. It is of interest also that each individual tends to show a distinctive pattern of hypoglycemic manifestations, and this pattern is apt to recur in successive attacks.

DR. ARANOW: The repetition of pattern is helpful because the patient often is able to recognize an impending attack and take appropriate measures. It will be noted that marked hypoglycemia causes symptoms particularly involving the central nervous system. This reflects the well established fact that glucose is the main source of energy for the central nervous system. Since a fire may be extinguished equally well by removing the combustible material or by excluding oxygen, it is not surprising that the symptoms and results of *hypoglycemia* and of *anoxemia* are almost identical—and are included in a single review article by Hoff et al.* This similarity is brought out strikingly by the pathological changes found in the brain of patients subject to recurring attacks of marked hypoglycemia. Dr. Wolf, who has made a careful study of this condition, will now describe these changes.

DR. ABNER WOLF: As Dr. Aranow has told you, the more severe changes in the brain in hypoglycemia resemble those seen in anoxia and that perhaps is the point which I would like to emphasize. The first slide (Fig. 2) will indicate this clearly.

You probably remember that one of the striking changes in nerve cells in the presence of anoxia is ischemic necrosis. When a patient suffers from severe hypoglycemia, and dies in an acute attack, ischemic necrosis may also be present, involving some of the nerve cells of the cerebral cortex, basal ganglia, and to a lesser degree other parts of the central nervous system. As a rule, however, such more serious changes probably do not occur. This may be deduced from the clinical facts, because the symptoms are reversible. But when they become irreversible, such degenerative changes in the nerve cells are encountered. Their bodies swell and their cytoplasm becomes hypereosinophilic. Their nuclei are contracted, hyperchromatic and sharply outlined. Such a cell is permanently damaged and will disintegrate. One observes exactly the same change with a reduction in oxygen supply to such elements or with inability to utilize oxygen. In addition, there is a variable degree of edema which you can see in this cerebral section.

Fig. 3 shows a section of cerebellum, this being the granular layer (indicating). Here you can see an ischemic necrosis of the Purkinje cells and definite edema of the tissue. Similar changes may occur in the nerve cells of the brain stem.

If convulsions are associated with the hypoglycemia, which is not infrequent as you have been told, one may find multiple acute perivascular hemorrhages in the brain. In some experimental work on the subject, this has been found to be an almost

* *Medicine*, 24: 161, 1945.

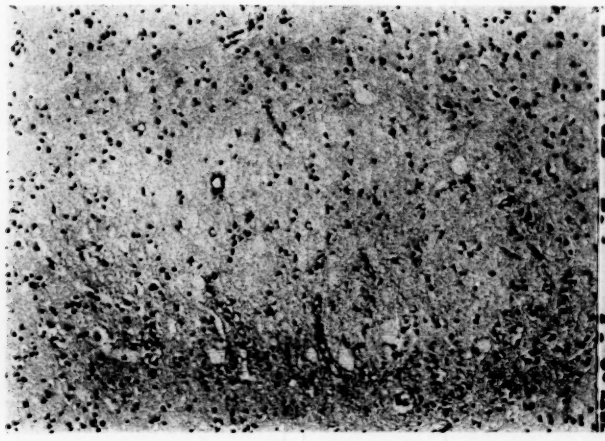

FIG. 2. *Cerebral cortex in a case of hypoglycemia with convulsive seizures induced by insulin shock therapy. Note focal area of recent ischemic degeneration with disappearance of many nerve cells and shrinkage of remaining cells.*

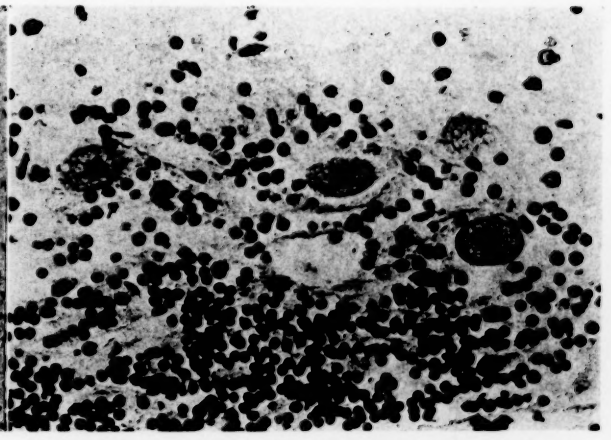

FIG. 3. *Cerebellar cortex in the same case. Four Purkinje cells undergoing acute ischemic necrosis are seen.*

constant feature of the more severe forms of this condition. However, in the majority of instances, the nerve cells show changes which are reversible. One of the commonest is the type known as chromatolysis in which the Nissl substance of the nerve cell breaks down and its body swells. This is a change which is completely reversible. The cell returns to its normal shape and Nissl content and normal function. The nerve cell, however, may become increasingly pallid and function at a lower degree of efficiency, a change which may become chronic.

If the patient suffers a great many hypoglycemic attacks of moderate degree, there may be more diffuse degenerative changes of a chronic type in the nerve cells. A section of the cerebral cortex will show that some of the nerve cells are shrunken, stain darkly and have condensed Nissl substance and pyknotic nuclei. The concentration of the nerve cell cytoplasm leads to a greater clarity of the outline of the apical dendrite. In an extreme degree of shrinkage, the cell may be reduced to a small element with a sinuous apical dendrite and is probably a poorly functioning or perhaps non-functioning unit. There may be focal areas of loss of myelin in the cerebral white matter. The subcortical white matter becomes pallid in this zone, indicating a partial loss of myelin sheaths.

After repeated severe hypoglycemic episodes, more particularly with convulsions, focal areas of nerve cell loss may be encountered in various parts of the cerebral cortex. One zone that may be involved is the hippocampus. A band of cells known as the subiculum is particularly prone to injury in anoxia and during convulsions. Such a focus of nerve cell loss in the frontal cortex may show replacement astrocytosis.

To summarize, we are dealing with a condition in which the histological changes are not specific. They resemble those seen in states of generalized or localized cerebral anoxia, or in conditions in which there is interference with the nutrition of the nerve cells.

DR. ARANOW: The sections which Dr. Wolf has shown us should enable us to avoid a common misconception. Undue emphasis has been placed upon the prompt relief of hypoglycemic symptoms by the injection of glucose. This relief is immediate when the hypoglycemia has been mild and of brief duration but we cannot expect the atrophy, edema and hemorrhages produced by longer and more severe blood sugar falls to vanish in an instant. When such changes

have occurred, symptoms may persist long after the level of the blood sugar has returned to normal.

Psychiatrists have studied some of the psychological aberrations produced by abnormally lowered blood sugar levels. J. Wilder has reported cases in which the patients have been confined to mental institutions for several years, diagnosed as psychotics, before it was discovered that the underlying mechanism was chronic recurrent hypoglycemia. Dr. Mayer-Gross made an interesting study of the psychological reactions in patients who were given insulin to produce hypoglycemic coma, following the mental reactions as the syndrome progressed through the five stages outlined above. Many crimes have been committed in states of mental aberration induced by unrecognized hypoglycemia and they range from disorderly conduct to rape, arson and murder. The number of such cases is large enough to make worth while, perhaps, the routine performance of blood sugar studies in criminals.

Let us now briefly review some of the laboratory evidences of functional cerebral change in hypoglycemia. Quastel, working with brain slices, showed that the synthesis of acetylcholine *in vitro* was possible only in the presence of glucose. Welsh discovered that the acetylcholine in the cerebral cortex of rats was strikingly reduced in amount in hypoglycemia. Gellhorn, Hoefer, as well as Brazier, have shown noteworthy changes in the electroencephalogram with hypoglycemia. The latter author recommends the administration of glucose about thirty minutes before the taking of an EEG in order to avoid possible misinterpretations due to lowered blood sugar.

Dr. Mason has made careful studies of von Gierke's disease, one of the interesting experiments which nature has provided for us. He has made significant contributions to the elucidation of its mechanism, so I shall ask him to discuss this disease in its relation to hypoglycemia.

DR. HOWARD MASON: I am presenting a patient whose metabolic difficulty is due to derangement of the carbohydrate cycle. How old is the child?

MOTHER: Five.

DR. MASON: The story is as follows: The patient weighed between six and seven pounds at birth and apparently was perfectly normal. She was given an artificial feeding and this was changed repeatedly as she did not take the feeding well and gained and grew very slowly. At one month of age she weighed seven pounds, at two months 7.2 pounds and at six months 13 pounds.

When she was four months of age she began to have generalized convulsions about once a week, always about six o'clock in the morning. After three convulsions she was taken to a hospital for study. During the month she was in the hospital she had one convulsion. The diagnosis of von Gierke's disease was made and she was discharged. A few days later she developed a fever and had another convulsion. She was then admitted to the Babies Hospital. The fever was due to an infection of the urinary tract and yielded promptly to sulfonamides. Then the problem was what to do about her metabolic disturbance. She was small for her age but well nourished. Her abdomen was unusually prominent and on the right side the liver extended down to the iliac crest. The surface and edge of the liver were smooth but firm. On the left side of the abdomen there was a mass which was thought to be an enlarged kidney.

Two epinephrine tests were performed. On neither occasion did the blood sugar rise. Then tolerance tests were done with glucose, levulose and galactose. The fasting blood sugar was always low. The glucose test did not show a maximum rise for two hours and then it fell steadily to

abnormally low levels unless she was fed again. The levulose and galactose tests showed rather low curves with rapid falls to normal and below. If we look now at Dr. Stetten's diagram of the carbohydrate cycle we can try to locate the point or points at which this patient has difficulty. The lack of rise in blood sugar after the administration of epinephrine means that there is difficulty somewhere in the breaking down of liver glycogen and the discharge of glucose into the blood stream. This is supported by the fact that the blood sugar falls to abnormally low levels when the patient is starved for only a few hours. Neither of these findings, however, locate the step at which the block occurs. The tolerance tests help us to do this. You will recall that the levulose and galactose tolerance curves were lower than normal. This means that the liver is able to remove these sugars from the blood and store them as glycogen in a normal manner. This in turn implies that the carbohydrate cycle from levulose-6-phosphate to glycogen is functioning properly. If this is true, then the only point where the patient can have trouble is in the dephosphorylation of glucose-6-phosphate or the phosphorylation of glucose to glucose-6-phosphate. The prolonged rise in blood sugar implied some possible difficulty in the phosphorylation of glucose. The dephosphorylation of glucose-6-phosphate in the liver is performed by alkaline phosphatase. Thannhauser analysed the livers from three patients with von Gierke's disease for phosphatase and found abnormally low amounts. This supports our conclusion as to the seat of the trouble.

We now knew that the patient's failure to gain and grow normally were probably due to prolonged periods of hypoglycemia when she was taking a regular diet at the usual intervals and that the convulsions were due to hypoglycemia. The problem seemed to be to retain her blood sugar nearer normal levels. We found we could accomplish this by feeding glucose or starch in some form at frequent intervals.

The result was that for four years and a half she has been fed more frequently than the normal child. At first we used glucose in the intervals between meals. Now we use dexin as well as regular meals. As time has gone on she has shown a tendency to improve, and whereas the family used to have to feed her several times during the night, she is now fed only once or twice. Is that not right?

MOTHER: Yes.

DR. MASON: You give her supper about what time?

MOTHER: About six.

DR. MASON: You feed her once or twice a night?

MOTHER: I give sugar before eight and one and five o'clock usually, but I have done away with the three o'clock feeding, if she does well.

DR. MASON: You say if she does well. Would you tell us what you mean by "if she does well"? Will you tell the doctors what you mean when she does not do so well? This child's mother has worked with her so long that she recognizes the symptoms of hypoglycemia long before the child gets into any trouble. Just tell the doctors what you mean.

MOTHER: I give what I call an average portion.

DR. MASON: What you do is to feed her during the night if she does not eat an average portion?

MOTHER: If she eats exceptionally well, that is, what I consider a very good portion, I can let it go until three o'clock.

DR. MASON: If she is going to get into difficulty what does she do?

MOTHER: She will temporarily lose her balance or she will suddenly become quite

irritable without any explanation. She responds to a drink of dexin and water.

DR. MASON: Do you want to ask any questions?

DR. ARANOW: No.

DR. MASON: Her liver is still way out of proportion to the rest of her body. The liver is still well down below the umbilicus on the right side.

The increased size of the liver in similar cases is due partly to stored glycogen and partly to stored fat. The percentage of each varies from patient to patient but is always well above normal.

These patients develop an acidosis when they are short of food for a few hours and when they have an infection. In fact these are the usual causes of death: infection and acidosis. During acidosis they excrete some ketones but as a rule the patient is worse and the CO_2 combining power is lower than the excreted ketones would warrant. We then determined the lactic acid content of this patient's blood on two different days. On both days she received her regular meals. One day in addition to her meals she received sufficient glucose between meals to hold her blood sugar at an approximately normal level. On the other day she received levulose instead of glucose. On the day she was given glucose the blood sugar height was nearly normal and the blood lactic acid content was only a little higher than normal, varying between 30 and 40 mg. per cent. On the day she had levulose the blood sugar was low (40 mg. per cent) to begin with and then fell to 14 mg. per cent. On this day the blood lactic acid was up to 150 to 160 mg. per cent. At the end of the period she was fed glucose and her blood sugar rose and the blood lactic acid started to fall.

One wonders where this lactic acid comes from. I wonder if it does not come from the liver. In these cases there is a tremendous demand, when the blood sugar is low, for the liver to break down glycogen. This liver, however, cannot break down its glycogen and free it as glucose but I wonder if it does not break it down and discharge it as lactic acid.

DR. ARANOW: Dr. Whipple, who has made major contributions to the subject, is going to discuss the curable, surgical types of hyperinsulinism. He has set up criteria to help differentiate them from the "functional" hypoglycemias. The most important of these criteria is the level of the fasting blood sugar. In situations in which excessive amounts of insulin are more or less continuously secreted, or in which glycogenolysis is seriously impaired, the fasting blood sugar levels are low. In so-called "functional hyperinsulinism," the fasting level is normal, and it is only after the ingestion of monosaccharides or simple polysaccharides (usually after three to five hours) that an abnormal fall occurs.

DR. ALLEN O. WHIPPLE: Dr. Aranow really prefaced my remarks by saying that I was to discuss the lesions which are benefited by surgical therapy, and my remarks are confined to that group of islet cell tumors producing hypoglycemia which are not amenable to conservative therapy but, if not carcinomatous, are amenable to surgical therapy.

The reason why I emphasize this point is that I probably see four or five patients who are sent with the diagnosis of possible islet cell tumor to one who has it. The diagnosis of islet cell tumor has been made in the majority of cases for two reasons: first, because what we speak of as the essential symptom triad of islet cell tumor is not understood and the second is that the diagnosis has been based upon a glucose tolerance test. It is on these two points that I wish to say a few words.

Dr. Aranow has spoken of certain islet cell tumors which do not produce the syndrome of hypoglycemia. That is true. The

largest islet cell tumor which we have removed, and which was called by the way a carcinoma, did not have any hypoglycemic symptoms and did not suggest in any way an islet cell tumor. This patient was operated upon after the Medical Service and the *X*-ray Service had joined us in the diagnosis of carcinoma of the pylorus or of the antrum. That patient has been followed now for almost six years. There is a question as to whether or not she has a recurrence but if she has one she is doing very well with it.

The islet cell tumors which produce the symptom complex of hypoglycemia, however, as a rule have a very definite picture. In the first place, these individuals present a symptom pattern. We speak of it as a pattern along the lines of the vasomotor system, the motor system, or the psychic system. A patient who has a pattern usually follows it regularly in the subsequent attacks. The patterns vary just as much as they vary in insulin shock with an overdosage of insulin. The size of the tumor does not apparently determine the severity of the symptoms except that the patients who have a carcinoma of the islet cells with metastases almost invariably have a much more severe type of hypoglycemia which is not amenable to even large doses of glucose. But with a patient who gives a definite pattern, before advising surgery we insist upon three things: First, the patient must give a history of having the attacks come on during the fasting stage; secondly, during the attack, or after a prolonged fast, the blood sugar must be below the level of 50 mg. per cent; and thirdly, the patient must come out of the attack or the pattern immediately on the administration of glucose. Unless these criteria are followed a great many patients will be explored unnecessarily.

One reason why the patients are explored is that the diagnosis is based upon a glucose tolerance test and that is the other point I want to emphasize. I do not care how you use the glucose tolerance test for other purposes; I insist that it is not an adequate test for making the diagnosis of islet cell tumor.

In studying these patients the method of determining their blood sugar levels should be as follows: They should be made to fast until they develop the pattern. The blood sugar should be taken then and they should be given glucose solution immediately. The administration of the glucose will bring them out of their pattern in an amazingly fast time, just as an individual in insulin shock is brought out of it.

To summarize the experience of the clinic here, thirty-nine patients have been explored for the purpose of searching for an islet cell tumor. Tumors have been found in thirty-one of these thirty-nine, or about 80 per cent. I may say that in another clinic where these criteria are not used, forty-two patients were explored and only sixteen had a tumor. Tumors were found then in thirty-one of these patients. They proved to be benign adenomas in twenty-six and questionably malignant in four, as judged from the microscopic sections, because of the presence of islet cells in the blood vessels and in the areas which were not encapsulated. These have been followed and none of them have proven to be malignant. We have had one case of carcinoma.

An interesting point is that in eight patients we have found a tumor at the second operation, and one reason for overlooking the tumor is the fact that in a great many instances in which the tumor is looked for the duodenum has not been mobilized. In order to feel these tumors—they average about the size of an ordinary marble or hazelnut—the duodenum has to be mobilized. Once one has palpated them they are easily distinguished. They have a very definite feel. They can be palpated with the fingers and thumb but not just over the surface of the pancreas. The pancreas has

to be mobilized in order to make sure of it. In many instances the tumor is visible and seen on the anterior surface of the pancreas. In many instances they appear on the head of the pancreas and cannot be palpated unless the duodenum is mobilized.

In six patients more than one islet cell tumor was found and we have had two patients in whom there has been an adenomatosis. Because of not finding a single tumor, a partial pancreatectomy was done in fourteen patients and a total pancreatectomy in one. Many of these partial pancreatectomies were done because of the difficulty of enucleating the tumor, or because of the possibility of more than one tumor; and in a number of instances the subtotal pancreatectomy was done because we were unable to palpate the tumor.

The operative mortality through this entire series was 12 per cent, and in the patients in whom the tumor was present it was 9 per cent. Two patients have been explored with the condition about which Dr. Aranow spoke, idiopathic postoperative hypoglycemia.

One patient with von Gierke's disease who proved to be very interesting was studied by Dr. Palmer and myself but did not survive the exploratory procedure.

Again let me emphasize that the follow-up results in the patients who do have islet cell adenomas are exceedingly good. We have a number of patients that we have followed now for ten years. They have not had recurrences of any of their patterns.

There are three reasons for advising surgery in patients who give the triad and who have islet cell tumors. One is that if these patients continue to have attacks over a long period of time cortical damage may be produced, as Dr. Wolf showed you. They do show areas of definite cell degeneration. We have two patients who were studied for periods of seven years before the operation. One of them has had to be committed to an institution for the insane, and one other patient has periods of considerable mental disturbance.

The second reason is that—and this is particularly important to the surgeon—these patients require an enormous amount of carbohydrate to prevent their developing their patterns. We had one patient who put on 100 pounds in a period of six months. He was a strong, big Irishman to begin with. That added 100 pounds did not help. We have two patients who have weighed over 250 pounds and one of them was only five feet tall. We have one patient who is at the present time in the hospital on whom we have done a total pancreatectomy because we were unable to find the tumor at the first operation. At one time she was eating sixty oranges a day.

The third reason for advising surgery in a patient who meets the requirements of the diagnosis is the fact that it is often difficult to be certain whether or not the tumor is benign or malignant. Whether these degenerate from benign to malignant tumors we do not know, but certainly in some instances the pathologist cannot tell us whether the tumor is benign or malignant, and we have to rely upon the follow-up studies to determine that point.

DR. ARANOW: A word in closing about the management of the non-surgical or functional types of hyperinsulinism. The goal is to avoid the post-prandial fall in blood sugar. This may be done by frequent intermediate feedings but these often lead to excessive weight gain. Another method is to choose a diet of such a type that the post-prandial fall is avoided or minimized. Dr. George Thorn has published a recent study on blood sugar levels following isocaloric high carbohydrate, high fat, and high protein meals. Each has a somewhat different effect, both the post-prandial rise and fall being greatest after a high carbohydrate meal, and least after a

high-protein feeding. A high protein diet, therefore, may be useful in the therapy of the functional hypoglycemias.

STUDENT: Dr. Whipple says that one criterion of islet cell adenoma is that the response to administration of glucose must be immediate and yet Dr. Aranow stated that the response to glucose may not be dramatic. How can these statements be harmonized?

DR. LOEB: If hypoglycemia is of short duration, the response is prompt; but if prolonged, and if nerve damage has occurred, the response naturally may be greatly delayed and focal signs may persist.

I should like to make one point about the use of high protein diets. This therapy can hardly be expected to prove of great value in patients with disturbances in the capacity to elaborate glucose from glucogenic amino acids. In these patients, small but frequent feedings of carbohydrate in the form of milk, bread, etc., may be necessary to control hypoglycemia.

SUMMARY

The blood sugar level is in dynamic equilibrium, ever changing because it is dependent upon the varying balance of supply and demand. The supply of glucose comes from three main sources: absorption of digested polysaccharides and monosaccharides from the intestinal tract, liver glycogen and, lastly, other carbon fragments derived from the glucogenic amino acids, body fat and fractions remaining from partially metabolized glucose. The first and last sources probably contribute the greater share.

The crucial step in glucose metabolism appears to be the phosphorylation of glucose, a reaction catabolized by the enzyme hexokinase:

$$\text{Glucose} + \text{adenosine triphosphate} \xrightarrow{\textit{hexokinase}} \text{glucose-6-phosphate} + \text{adenosine diphosphate}$$

The Coris have recently shown that this reaction is specifically inhibited by a substance obtained from the anterior lobe of the pituitary gland. This inhibiting effect is blocked by insulin and prolonged by certain adrenocortical steroids.

Certain mechanisms may be suggested as operating to produce the hypoglycemia observed in various clinical disorders. Decreased absorption of glucose from the intestinal tract due to starvation or to disease of the small intestine may result in hypoglycemia, obviously because of a lowered supply. In myxedema, low blood sugar levels develop apparently because of marked slowing of the rate of passage of glucose through the intestinal mucosa. Liver glycogen is reduced not only by inadequate exogenous supply (starvation) but also from endogenous failure, as in Addison's disease; and finally by excessive utilization, as with long continued, strenuous physical effort. When the liver has been largely destroyed there may be insufficient formation and storage of glycogen. Von Gierke's disease appears to occupy a somewhat special position wherein the glycogen content of the liver is above normal but cannot be made available as glucose, hence the blood sugar values fall.

In hyperinsulinism (whether due to insulin overdosage, or to endogenous overproduction by islet tumors or to other causes), the blood sugar level falls apparently because the inhibiting pituitary effect on the hexokinase reaction is blocked, at least in part, by excess insulin and the reaction is therefore accelerated. Hypoglycemia occurring in adrenal cortical insufficiency appears to be due in part to a disturbance in gluconeogenesis from certain of the amino acids.

The symptomatology of hypoglycemia is diverse. In its mildest form the complaints are vague: weakness and a disinclination for physical and mental exertion. More

severe episodes are characterized by congestion or pallor of the face, sweating, palpitations, hunger, thirst, tremors and anxiety. These may be followed by difficulties in speech and uncoordinated movements and finally by convulsions, paralysis and coma. The pattern of symptoms may be very different in different individuals but the characteristic train of symptoms in any one individual is apt to be recurrent.

Chronic hypoglycemia of severe degree may result in damage to the central nervous system, the changes observed resembling those seen in anoxia. Edema, chromatolysis and perivascular hemorrhage, at first reversible, occur. Later there is death of nerve cells, replacement by astrocytes and loss of myelin, constituting permanent damage.

Acute hypoglycemic shock is treated by intravenous administration of glucose. The response is usually prompt and dramatic. In chronic cases with irreversible damage to the central nervous system, however, the effects may be slow and disappointing.

The aim of treatment in chronic, functional hypoglycemia is to supply a steady, slowly available dietary source of glucose. This is usually accomplished by small but frequent feedings of carbohydrate-rich foods. High protein diets, which cause a less marked post-prandial rise and fall in blood sugar, may be advantageous in some cases.

Hypoglycemia due to islet cell adenoma or hypertrophy is amenable to surgical treatment. To avoid futile explorations, however, it is necessary to rule out "functional" hypoglycemia occurring in individuals who, for obscure reasons, have an unusually pronounced post-prandial fall in blood sugar, not due to islet tumors. To make this important differential diagnosis, too much reliance should not be placed on the glucose tolerance test; if employed, it should be borne in mind that organic hypoglycemia appears on fasting whereas the functional types show low blood sugar levels most frequently three to five hours after ingestion of glucose.

The following triad is suggested as indicating exploration: (1) a repeated individual symptom pattern coming on in the fasting state; (2) a blood sugar concentration below 50 mg. per cent during an attack, or after a prolonged fast; (3) in earlier stages, relief of an acute episode by administration of glucose. When these criteria are fulfilled, careful search by the surgeon, after mobilizing the pancreas, will almost always be successful.

Clinico-pathological Conference

Fever of Unknown Origin*

Stenographic reports, slightly edited,† of weekly clinico-pathological conferences, held in the Barnes Hospital, will be published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, L. P., a forty-two-year old butcher, entered the Barnes Hospital on May 25, and died on May 31, 1946. His chief complaints were drowsiness, cough and headache. The family history was irrelevant. Since childhood, the patient apparently had been in good health with the exception of an accident two years prior to admission when he fell on his head; since then, he had had numerous frontal headaches and a backache. He lived on a farm and slaughtered his own cattle, the last time about one week before the onset of his recent symptoms. He was vaccinated against smallpox in childhood and received injections, probably against typhoid fever, at the age of sixteen. Two weeks before admission he had acquired many tick bites while in a pasture. The water supply at his home came from city sources and he was not accustomed to drinking milk.

For six to eight months before admission, according to a member of his family, the patient had developed increasing drowsiness and tended to fall asleep easily even while conversing. At night, he exhibited considerable restlessness. At the onset of these symptoms, he began to have a cough and on several occasions produced some bloody sputum. There had been no anorexia or loss of weight during this period. Five days before entry, he suddenly developed vague generalized soreness and aching, felt feverish but had no chills. He lost his appetite, developed a severe headache and became very drowsy. The following day fever persisted and he had a questionable chill. He was admitted to a rural hospital. While there, sulfadiazine, sulfamerazine, sulfathiazole, neoprontosil and penicillin were given, all without effect, and he continued to have fever. A lumbar puncture was done and the spinal fluid was said to have been entirely normal. He was then sent to the Barnes Hospital.

Physical examination revealed the following: Temperature 40°C., pulse 90, respirations 20, blood pressure 150/80. The patient was an obese white male who appeared drowsy and lethargic. He answered questions rationally when aroused. The pupils were small but reacted to light and accommodation; they were regular and equal. The eye grounds showed only slight venous engorgement. The ears were normal. There was slight injection of the pharynx and the tonsils were enlarged. The trachea was in the mid-line. The lungs were clear anteriorly, but posteriorly there was some dullness to percussion and many coarse râles were heard over the left lower lobe. The heart was not enlarged to percussion. The rhythm was regular. There was a grade II systolic murmur at the apex. Radial pulses were equal and regular. The abdomen was obese. There was no tender-

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† By Robert J. Glaser, M.D.

ness or resistance. The liver edge was felt 6 cm. below the right costal margin. The spleen was not palpated. Neurological examination was recorded as normal.

Laboratory findings on entry were as follows: Blood count: red cells, 5,000,000; hemoglobin, 15 Gm.; white cells, 12,800; differential count: basophiles 1 per cent; eosinophiles, 1 per cent; "stab" forms, 34 per cent; segmented forms, 54 per cent; lymphocytes, 10 per cent. Urinalysis: albumin 1+; acetone, negative; microscopic, negative. Urine culture: very few colonies of Escherichia coli. Stool examination: guaiac, negative. Stool culture: no pathogenic organisms. Kahn reaction: negative. Blood culture: no growth. Blood chemistry: non-protein nitrogen, 26 mg. per cent; sugar, 74 mg. per cent; total proteins, 6.8 Gm. per cent; albumin, 3.6 Gm. per cent; globulin, 3.2 Gm. per cent. Sputum examination: No acid fast organisms seen. Sputum culture: alpha and beta hemolytic streptococci; mouse inoculation, negative. Agglutination tests: typhoid ("H" antigen): 4+, 1:40; 1+, 1:320; paratyphoid, tularense, brucella, and proteus ox-19, negative. Lumbar puncture: normal dynamics; fluid, clear; 2 lymphocytes; protein, 20 mg. per cent; sugar, 66 mg. per cent; sodium chloride, 665 mg. per cent; colloidal gold curve 0000000000; Wassermann, negative. Smear of sediment: no organisms; culture: negative. Roentgenogram of the chest: indeterminate.

Blood cultures were taken twice daily, and all were sterile. Two days after admission, diminished tactile fremitus over the right posterior lung field and dullness to percussion at both lung bases were noted. Over these areas there were diminished breath sounds which were bronchial in character. Throughout both lungs moist râles were heard. A roentgenogram of the chest at that time revealed infiltration along the descending bronchi on the left, adjacent to the cardiac silhouette. The interpretation was: "pneumonia, left lung." At this time, the pulse rate was 88 and the temperature 40°C. The icteric index was reported as 24. A skin test for lymphopathia venereum was negative. The urine showed 2+ albumin and microscopic examination was normal. The white blood cell count was 13,000 with 22 "stabs," 60 segmented forms, and 18 lymphocytes. The temperature after the second day remained above 40°C. and the patient was lethargic and at times irrational. On the third hospital day, a palpable spleen was noted. The liver edge was felt persistently 6 cm. below the costal margin. The signs in the lungs did not change. On the third day, a test for cold agglutinins was negative; agglutinins for the typhoid "O" antigen were reported as being 1+ in a dilution of 1:20; and for tularemia 1+ in a dilution of 1:160. Agglutination tests for the other organisms recorded previously remained negative. A skin test for coccidioidomycosis was negative at twenty-four and forty-eight hours. No malarial parasites were seen in the blood smear. The clinical findings remained essentially unchanged; high fever and lethargy persisted. Further laboratory examinations showed the cephalin-cholesterol flocculation test to be 3+, and the van den Bergh, 2.9 mg. per cent direct, 3.6 mg. per cent indirect—D/I ratio 80 per cent. Urobilinogen in the urine was negative, bile was present in one specimen and absent in another. Typhoid agglutinins ("H" antigen) on the day of death reached a titer of 1:5120. The carbon dioxide combining power was 59.9 volumes per cent, the blood chlorides 92 m.eq./l. A neurologic consultant saw the patient and considered the findings consistent with a non-specific encephalopathy. The patient became slightly jaundiced and gradually lapsed into unconsciousness. He then suddenly went into profound peripheral vascular collapse, and supportive therapy was unavailing. The white cell count on the day

of death was 14,000. The patient received penicillin throughout the hospital course, and streptomycin was started on the day before his death.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This case presents a difficult problem. It is one which concerns fever of unknown origin in a patient who was obviously acutely ill. In the history it is stated that six to eight months prior to admission he developed lethargy and drowsiness. He would fall asleep in the middle of a sentence. Concomitantly, he developed a cough with bloody sputum. There is only an incomplete record of these early symptoms, the story having been obtained from the family because the patient was too ill to be questioned. Then five days before admission he developed the final acute illness that has been described. If we are to correlate these two sets of symptoms, we must inquire as to what diseases will begin with drowsiness, cough and bloody sputum, remain reasonably latent and then rather suddenly exhibit an acute exacerbation. Are there suggestions?

DR. CARL G. HARFORD: In view of the cough and hemoptysis I would suggest miliary tuberculosis.

DR. ALEXANDER: Would you specifically designate the original episode, which occurred six months previously, as miliary tuberculosis?

DR. HARFORD: No. The patient may first have had pulmonary tuberculosis, and the lesion may have eroded into a blood vessel at the time of the final illness.

DR. ALEXANDER: In view of the fact that there were indications of beginning pneumonia would you be willing to consider the diagnosis of tuberculous pneumonia?

DR. HARFORD: I think that diagnosis would fit the symptoms very well.

DR. ALEXANDER: In any fever of unknown origin one must, of course, consider tuberculosis. The patient had a cough, blood-streaked sputum, definite pulmonary signs and a negative blood culture. What about his blood count, Dr. Moore? Is that compatible with acute miliary tuberculosis?

DR. CARL V. MOORE: Yes. Usually, however, there is a higher monocyte count with actively progressing tuberculosis.

DR. ALEXANDER: Does anyone wish to pursue the idea of tuberculosis further? Is there anything against the diagnosis of tuberculosis?

DR. W. BARRY WOOD, JR.: How would one explain the headache and drowsiness preceding the acute episode if the patient had pulmonary tuberculosis complicated by a miliary spread five days before he entered the hospital?

DR. ALEXANDER: I do not know. I presume that they might have been due to fever. What is your opinion, Dr. Harford?

DR. HARFORD: He had had a blow on the head, you will remember, two years before. He may have had some intracranial lesion. A diagnosis separate from that of tuberculosis would have to be made, however.

DR. ALEXANDER: There is a great deal in favor of the diagnosis of tuberculosis. If this is not tuberculosis, what else might relate the early symptoms to the final acute illness?

DR. HAROLD BULGER: Encephalitis lethargica could explain the long course. Five days before his entrance into this hospital the patient could have suffered an acute exacerbation.

DR. ALEXANDER: Yes, this man might have had encephalitis lethargica. He was lethargic, certainly. Dr. Harford, what specifically did you have in mind when you called attention to the blow on the head and his headache?

DR. HARFORD: I was suggesting that the patient might have had a subdural hemorrhage two years previously.

DR. ALEXANDER: That might have made

him drowsy. Would you connect this with the acute episode?

DR. HARFORD: No, the blow on the head could explain only the encephalitic manifestations.

DR. OLMSTED: Can a diagnosis of encephalitis be made with a completely negative spinal fluid?

DR. ALEXANDER: Dr. Bulger, you brought up the diagnosis of encephalitis. Would you like to answer that question?

DR. BULGER: I do not believe that there are any cases of encephalitis reported with a completely normal spinal fluid. That point, I agree, makes the diagnosis of encephalitis untenable.

DR. HARFORD: There have been some cases reported with a normal cell count but I believe the spinal fluid protein is always elevated in such cases.

DR. ALEXANDER: Are there any other suggestions?

DR. PALMER H. FUTCHER: Dr. Alexander, another diagnosis to consider is bronchiectasis with secondary brain abscess.

DR. ALEXANDER: That is a good suggestion. Both hemoptysis and cough are signs of bronchiectasis. An infected embolus to the brain, causing a brain abscess, could explain the acute phase of the illness, and could afford a means of correlating the long standing symptoms with the terminal ones.

DR. C. V. MOORE: Dr. Alexander, we do not know just how much blood the patient brought up, nor do we know that he actually had a hemoptysis. He coughed and brought up some blood which might have come from his nose.

DR. ALEXANDER: That is correct. Our information on this point is incomplete. However, we must consider the possibility that the patient had a hemoptysis and accordingly the suggestions have been made that the bleeding was caused by either tuberculosis or bronchiectasis.

DR. WOOD: Dr. Alexander, although it is well to consider carefully all the diagnoses so far suggested, I think that they can all be ruled out on the basis of the clinical course of the final acute illness.

DR. ALEXANDER: How would you rule out suddenly precipitated tuberculous pneumonia?

DR. WOOD: The sputum was negative for tubercle bacilli and the patient developed jaundice. We would expect the sputum to be positive if this were acute tuberculous pneumonia. Jaundice certainly is an uncommon finding in tuberculosis.

DR. ALEXANDER: I agree that the presence of jaundice casts doubt upon the diagnosis of tuberculosis. What other illness could explain the patient's symptoms?

DR. H. L. WHITE: I think that the long-standing symptoms had nothing to do with the cause of death and believe that the patient died of infectious hepatitis. There is no way to prove this diagnosis but everything seems to me to be compatible with it.

DR. ALEXANDER: Would the evidence of pneumonia be compatible with the diagnosis of infectious hepatitis?

DR. WHITE: It is not uncommon for patients with infectious hepatitis to develop pneumonia.

DR. ALEXANDER: Dr. Wood, are you attracted to this idea?

DR. WOOD: I believe it is a very good suggestion, Dr. Alexander, and a difficult one to exclude; however, I do not think that infectious hepatitis is the correct diagnosis. Some change in the pulmonary manifestations of the disease should have occurred with penicillin therapy if they had been due to secondary bacterial pneumonia. This point is, of course, only indirectly against the diagnosis of infectious hepatitis.

DR. CHARLES H. EYERMANN: I would suggest that these symptoms, including the hemoptyses, are not inconsistent with typhoid fever.

DR. ALEXANDER: Yes, in fever of un-

known origin, typhoid is another one of the diseases which must be considered. Dr. Eyermann, please tell us what suggests this diagnosis.

DR. EYERMANN: The results of the agglutination tests.

DR. ALEXANDER: The "H" agglutinins increased from a dilution of 1 to 40 to one of 1 to 5,000. The "O" agglutinins were recorded as positive in a dilution of 1 to 80. What about this discrepancy? Is the high value for the "H" agglutinins significant, Dr. Harford?

DR. HARFORD: The patient probably received typhoid vaccine twenty-six years ago. During febrile illnesses it is known that the anamnestic response is more likely to raise "H" agglutinins than "O" agglutinins. I think that, in view of the many negative blood and stool cultures, the "H" agglutinin response was probably due to an anamnestic reaction.

DR. ALEXANDER: Agglutinations were repeated on the seventh day of his illness. Would you expect an "O" agglutinin titer of 1 to 80 on the seventh day?

DR. HARFORD: It is difficult to explain the "O" agglutinins. I would have expected a negative test for "O" agglutinins at this time, if the patient did not have typhoid fever. However, I should like to emphasize the fact that this man had frequent blood cultures and he also had many stool cultures, all of which were negative. A patient with severe typhoid fever should have organisms in either the blood or the stool during the early phase of the disease.

DR. ALEXANDER: This man did have, however, a high fever with a slow pulse, headache, lethargy, splenomegaly and the high agglutinins; these findings are certainly suggestive of typhoid fever. Dr. Eyermann, do you think that the onset was too sudden for typhoid?

DR. EYERMANN: Yes, but almost anything can happen in this disease. There certainly may be pneumonic signs.

DR. ALEXANDER: What other diseases may conform to this picture?

DR. HAROLD SCHEFF: I think one would have to consider brucellosis, despite the rapid course.

DR. ALEXANDER: This man was a butcher who slaughtered his own cattle. Such a history should always bring to mind the diagnosis of brucellosis.

DR. SCHEFF: Against the diagnosis, of course, are the negative agglutination tests.

DR. ALEXANDER: Are there other suggestions?

STUDENT: Tularemia should be considered.

DR. ALEXANDER: That is a good suggestion. If the patient had tularemia, would you expect a portal of entry to be manifested?

STUDENT: Not in the typhoidal type of tularemia.

DR. ALEXANDER: Why should this farmer have gotten the typhoidal type of tularemia?

STUDENT: There was a history of tick bites.

DR. ALEXANDER: May a tick bite be the portal of entry?

STUDENT: In some cases I believe it has been proved to be.

DR. ALEXANDER: That is correct. There is no description of lymphadenopathy; apparently he did not have any, either localized or generalized. If he were bitten by a tick and the tick bite were considered the portal of entry, the clinical picture might still be that of the typhoidal form of tularemia. What else is there in favor of the diagnosis?

STUDENT: The agglutinations afford important evidence, and it is particularly notable that the titers increased.

DR. ALEXANDER: Yes, they were negative at the onset and later became positive in dilutions up to 1 to 160. Dr. Wood, is this rise in the titer of significance?

DR. WOOD: Yes, and also it occurred at exactly the expected time.

DR. ALEXANDER: I believe that it is generally believed that such a rise in agglutinins is the best diagnostic sign next to recovery of the organisms from the blood.

DR. HARFORD: That is correct. It is of interest to note, however, that in one recorded epidemic of tick-borne tularemia there were no instances of the typhoidal type.

DR. ALEXANDER: This man could have eaten an infected rabbit. One can acquire the disease by way of the gastrointestinal tract and localized lesions, though not apparent, can be found in the gastrointestinal tract on pathologic examination. What about pulmonary manifestations in tularemia?

STUDENT: I do not believe that they are common, but perhaps those of the present case could be explained on the basis of a secondary pneumonia.

DR. ALEXANDER: No, that is incorrect. There may, of course, be a secondary pneumonia but tularemic pneumonia, *per se*, is common.

DR. BERTRAND Y. GLASSBERG: Is not the roentgenologic picture of tularemic pneumonia said to be diagnostic?

DR. DONALD S. BOTTOM: No, I do not think so; I believe, however, that this patient's roentgenogram is in keeping with those seen in tularemic pneumonia.

DR. ALEXANDER: We are collecting some very strong evidence here in favor of this diagnosis. What fact, other than that in the tick-borne variety it is not common to see the typhoidal form, is against the diagnosis of tularemia?

DR. WOOD: The incubation period, if the history was correct, was nine days, which is a little longer than usual.

DR. FUTCHER: Rickettsial disease should be considered in view of the history of a tick bite; but the absence of a rash and the negative OX-19 agglutinations are against the diagnosis.

DR. ALEXANDER: Yes. As you have pointed out, however, it is extremely rare to have either Rocky Mountain spotted fever or typhus fever without an eruption. The description of the patient was not suggestive of rickettsial disease either. Patients with spotted fever are flushed, have conjunctivitis, a fast pulse and rapid respirations.

DR. WOOD: I would like to emphasize that several other points favor the diagnosis of tularemia. The white blood count was elevated and repeated blood cultures were negative on the usual bacteriological media.

DR. ALEXANDER: What medium should be used to culture B. tularense?

DR. WOOD: Cystine blood agar is a satisfactory medium, and it is the one we use in this laboratory. It was not, however, used in this case. Also the continuous high fever for the last three days of the patient's life, and the final episode during which the patient became jaundiced and then comatose, describe perfectly the terminal phase of bacteremic tularemia. According to Foshay* the terminal bacteremia usually results from a small tularemic tubercle rupturing into a blood vessel, and the patient almost invariably dies within a few days. Thus the course of the final phase of this patient's illness and the pulmonary findings fit in very well with the diagnosis of tularemia.

STUDENT: Dr. Alexander, you mentioned the possibility of a patient's acquiring the disease by eating infected rabbit meat. I thought that the organisms were killed by cooking.

DR. ALEXANDER: Yes, if the meat is thoroughly cooked, but frequently the disease is contracted from eating improperly cooked rabbit.

* FOSHAY, L. Tularemia: A study of certain aspects of the disease including methods for early diagnosis and the results of serum treatment in 600 patients. *Medicine*, 19: 1–83, 1940.

STUDENT: If this were tularemic pneumonia, would one not expect to find large mediastinal lymph nodes?

DR. ALEXANDER: This man died in a very early stage of the disease. If he had survived longer, I think he would have developed such nodes.

STUDENT: In view of the lethargy of six months' duration, could this have been chronic tularemia with an acute exacerbation?

DR. WOOD: Not with a negative agglutination test on entry.

DR. ALEXANDER: In summary, it would appear, from the foregoing discussion, that the clinical data in this case favor the diagnosis of tularemia.

Final Clinical Diagnosis: Tularemia.

PATHOLOGIC DISCUSSION

DR. ROBERT A. MOORE: This man had pulmonary disease. On the left side there was lobar pneumonia and on the right side bronchopneumonia. The pneumonia apparently contained a great deal of fibrin inasmuch as, in the gross, it was grey and yellow. It was also a necrotizing type of pneumonia for there was one large focus, 28 mm. in diameter, in which the tissue was yellow and had undergone complete necrosis. This process was associated with what appeared to be foci of necrosis, several millimeters in diameter, in the liver and spleen. At the time this autopsy was done we were confronted with exactly the same two problems that were raised by Dr. Alexander. First, was this an acute phase of an illness that the patient had for a long period of time or did he have two separate diseases? That question can be answered by saying that no anatomic changes in any of the tissues, grossly or microscopically, indicated that the patient had anything more than an acute illness, the duration of which was a few days or a few weeks. Whatever the cause of his drowsiness and his blood tinged sputum could have been, there was no evidence in the autopsy material bearing on it.

The second important problem concerns the relation between the pneumonia and the disease in the remainder of the viscera. That relation could have been any one of three: In the first place, there could have been two separate diseases, as has been pointed out, and the pneumonia could have been a terminal event in some other disease; second, this could have been a disease of which pneumonia was a part; or, third, pneumonia could have been the primary disease and the other findings secondary to it. The last idea seemed rather unlikely inasmuch as this pneumonia was of the necrotizing type. The only complications that I could imagine in the viscera in a primary pneumonia would be abscesses, and the lesions in the liver and spleen did not have the character of abscesses. They were foci of solid coagulation necrosis rather than of suppuration. Such foci in the liver and spleen, especially after the diagnosis of typhoid was suggested, certainly aroused interest in the possibility, not of typhoid, but of paratyphoid fever, inasmuch as the foci of necrosis in typhoid are usually extremely small, while those in some of the Salmonella infections, and in paratyphoid B particularly, can be as large as they were in this patient. On the other hand, there were no lesions in the gastrointestinal tract. If this had been typhoid or paratyphoid one would have expected to see profound edema of the submucosa of the small and large intestines, especially of the large intestine in paratyphoid B, and there would have probably been typhoid or paratyphoid organisms in the lesions in Peyer's patches. Thus, with the gross examination two possibilities were left: that these splenic and hepatic lesions were completely separate, or that they were part of a disease of which pneumonia is also an integral part.

FIG. 1.

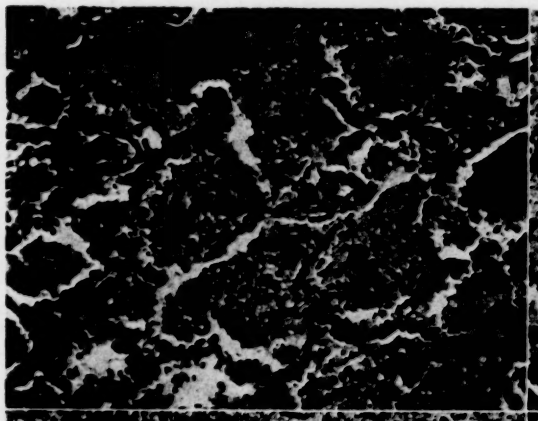

FIG. 2.

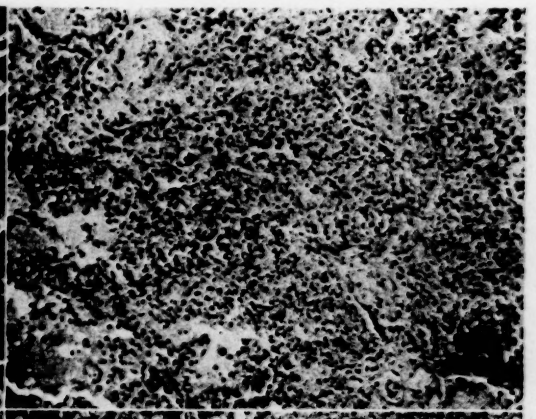

FIG. 3.

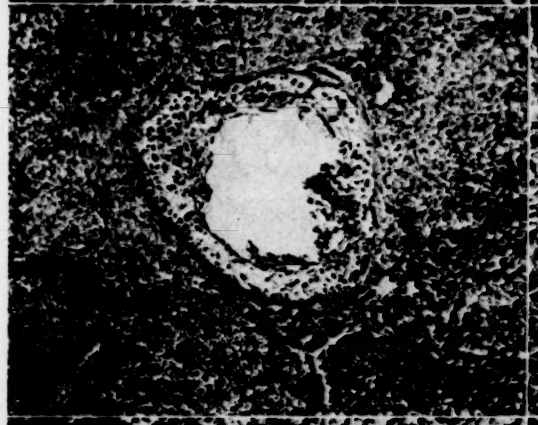

FIG. 4.

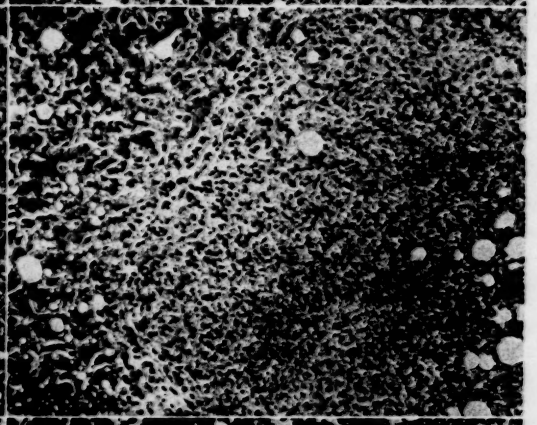

FIG. 5.

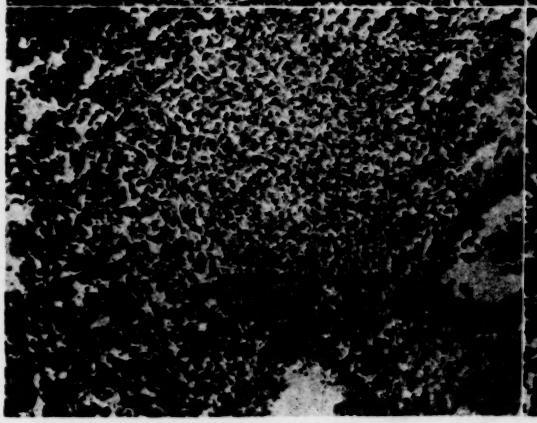

FIG. 6.

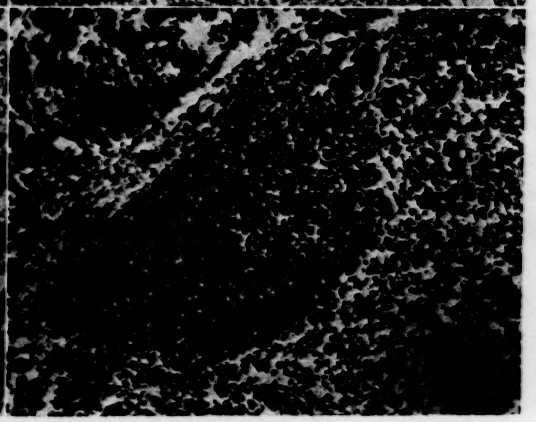

FIG. 1. *Low power view of a section of the lung, showing an area of pneumonia. The alveolar walls are intact; the exudate contains a relatively small number of cells, mostly mononuclear.* × 47.

FIG. 2. *Low power view of a section of the lung showing another area of pneumonia. Note that the alveolar walls on the left are intact while those to the right are undergoing necrosis.* × 47.

FIG. 3. *High power view of a section of the lung showing an artery. There is edema of the sub-intimal layer and mononuclear infiltration.* × 97.

FIG. 4. *Low power view of a section of the liver showing a focus of necrosis.* × 47.

FIG. 5. *Low power view of a section of the spleen showing a focus of necrosis.* × 47.

FIG. 6. *Low power view of a section showing a focus of necrosis in a lymph node.*

The microscopic studies afforded additional information on the nature of these lesions. Figure 1 is a characteristic microphotograph of the pneumonia. It is seen that the alveolar walls were intact; the pneumonic exudate consisted of fluid and fibrin with only a few cells—relatively few cells as compared with a typical pneumonia, and many of them were mononuclear cells. These observations immediately throw considerable doubt on the premise that this was an ordinary terminal bronchopneumonia complicating some other disease; that kind of pneumonia is usually caused by the staphylococcus or the streptococcus, and is characterized by exudation of large numbers of polymorphonuclear leukocytes into the alveoli. In other regions (Fig. 2) there was a different type of pneumonia. On one side the alveolar walls appeared normal and in another region they were undergoing necrosis. In other words, in addition to the large focus of necrosis which was seen in the gross, there was necrosis throughout many small foci in the lung. The exudate was undergoing necrosis and so were the alveolar walls. There was no evidence of chronicity in this disease and it is of some importance, even at this stage in the analysis, to see that the necrosis was not associated with any profound reaction immediately about it. Also the necrosis had the characteristic of causing disruption of nuclei, and many small karyorrhectic particles were seen throughout the tissue.

In Figure 3, definite evidence of an endarteritis was seen, characterized by a mononuclear cell infiltration with edema.

In the liver (Fig. 4), largely in the portal spaces, though not exclusively there, large foci of necrosis were present. Again, as in the lung, the notable features were karyorrhexis of the nuclei, coagulation of the tissue, and little or no reaction about the foci. The absence of a fibroblastic response was striking.

Figure 5 shows a nodule in the spleen in which there was a focus of necrosis; the lesion was perhaps less advanced than the one in the liver, but the salient features were the same.

In Figure 6, a lymph node which showed the same pathologic changes is seen. Many of the necrotic foci in the node were in the periphery, flattened out against the surface of the capsule but within the substance of the node.

Finally, in the brain, there was very slight cellular infiltration into the perivascular spaces in a few areas, but this was not conspicuous.

At the time of autopsy, the diagnosis of tularemia was considered. Examination revealed foci of necrosis in the liver, the spleen, and the lymph nodes, and a pneumonia of the necrotizing type in which microscopically the exudate was found to have consisted of mononuclear cells. Therefore, a final diagnosis of tularemia was made on the basis of the history of a tick bite, the consistency of the clinical observations, the ascending titer of agglutinins and the anatomic changes.

Many of the tissues were stained for bacteria in an attempt to find organisms, since occasionally a few small gram-negative rods can be seen in a necrotic focus. None were found here, and no attempt was made to recover the organism, because of the dangers attendant upon handling B. tularense in the laboratory. The diagnosis of tularemia, though resting on the clinical observations and the histologic findings, would nevertheless seem to be clear.

Final Anatomical Diagnoses: Tularemia; lobar pneumonia of the lower lobe of the left lung, with focal necrosis; serofibrinous pleurisy of the left lung (200 cc.); bronchopneumonia of all lobes of the right lung; foci of necrosis in the liver, spleen and lymph nodes; hyperplasia of the spleen (650 Gm.); hyperplasia of the hilar and portahepatic lymph nodes, and hepatomegaly (3000 Gm.).

Case Report

Cranial Arteritis*

A Review of the Literature with Report of a Case with Total Blindness

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CRANIAL arteritis, or "temporal arteritis," as it was originally named, was first described by Horton, Magath and Brown in 1932,[1,2] since which time forty-one cases have been reported in the literature. The syndrome is well defined, consisting of signs and symptoms referable to inflammation of the temporal arteries and other branches of the carotid artery, with constitutional effects suggesting a low-grade subacute or chronic infectious process. The disease has been observed only in the older age group of the white race, the age extremes of reported cases being fifty-five[1] and seventy-six.[15] Females have predominated among those affected.

A careful study of the published case reports reveals a striking similarity in the clinical and pathologic aspects of the disease, which has led most authors to the belief that this is a specific entity. An analysis of the following description of the disease and the study of the case herewith reported would seem to support this belief.

Etiology and Pathogenesis. All authors have called attention to the similarity of this process pathologically, and to a much lesser extent, clinically, to periarteritis nodosa. In fact, Kilbourne and Wolff[17] mention a case of proved periarteritis nodosa in which temporal arteritis was present. Microscopically, both diseases show panarteritis, and some workers state that histopathological differentiation is not possible.[5,17] This view is not accepted by most authors, who believe that certain characteristic differences make diagnosis possible in most cases.[2,4,16] Clinically, differentiation offers little difficulty, inasmuch as cranial arteritis is a relatively benign condition, usually self-limited in duration. Furthermore, there is no clinical evidence of inflammation of the smaller visceral arteries corresponding to the asthma, hypertension, neuritis and nephritis of periarteritis nodosa.

An allergic origin has been considered, but this seems unlikely in view of the absence of an allergic history, the age of these patients and the lack of eosinophilia.

The majority of those who have studied this disease have reasoned that the local and systemic signs and symptoms are those of a low-grade, subacute infection. In many of the reported cases, there has been found infection in the mouth or head. Infected teeth have been present in nine cases; Horton's second patient[1] recovered after his infected teeth were extracted, while one of Profant's patients[15] experienced a severe exacerbation after removal of three infected teeth. Sinusitis,[16] pharyngitis, cervical adenitis[7,13] and infections of the gums[4,17] have also been reported. In view of these findings, plus the fact that the first symptom may be pain in the teeth, jaw or neck, Kilbourne and Wolff[17] have suggested the possibility of direct extension of local infection into neighboring arteriosclerotic arteries. In spite

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of careful search no constant organism has been found in the diseased tissue.

Clinical Picture. Compatible with the concept that this is a chronic or subacute infection are the findings of a generalized systemic reaction in every case. The onset may be insidious[17] or sudden as in the case here reported. General malaise, weakness and lassitude are constant. Anorexia, and loss of weight which is probably due to the anorexia and the frequent pain on mastication are prominent. The weight loss may be as much as thirty pounds, as in Sprague and MacKenzie's case.[9]

Low grade fever is probably present at some time in all cases, although its absence was noted in the case reported by Shannon and Solomon.[16] The temperature usually ranges from 98 to 102°F., the highest recorded temperature being 103°F.[1] Shaking chills are uncommon, but sweating is often prominent in the earlier stages.

The local signs and symptoms more directly related to the arteritis usually appear concomitantly with the systemic reaction, although in approximately one-fourth of the cases, they have lagged behind the onset of malaise, fever and anorexia. Often there is aching pain in the jaws, teeth, ear, cheek or neck even before temporal pain and headache begin. Severe, throbbing headache, generally frontotemporal in location, with tenderness of the scalp has been observed in every case. It is usually steady, but may be paroxysmal in nature. Pain on mastication has been present in more than half of all cases;[15] swelling and tenderness of the face and mucous membranes have been found often.[3,7,17] The appearance of visible and palpable changes in the temporal arteries, which establishes the diagnosis, usually occurs one to two weeks after the onset of headache and constitutional symptoms. This important sign may appear, however, in a few days[6] or not for as long as nine months.[26] The vessels become very prominent, thickened, and tortuous, and are usually nodular; pulsation commonly disappears. There is inflammation of the contiguous tissues, with marked hyperalgesia. The acute inflammation may last for three weeks to three months,[26] after which the arteries slowly appear to return to their original uninvolved state. Exacerbation of the acute arteritis has occurred several times,[1,15] once after extraction of three infected teeth.[15]

It has been stated that involvement of the retinal arteries is not a common complication.[16] However, a careful perusal of the literature reveals that fourteen patients of the forty cases reported have suffered definite visual impairment. One case report merely mentions blurring and "poor vision in one eye" without further explanation.[7] In another report it is stated that there was "some deterioration of eyesight."[26] Three patients lost vision in one eye,[7,14,26] one had partial loss of vision with field constriction in both eyes,[22] three remained blind in one eye, with partial blindness in the other eye,[5,11,14] while five suffered complete loss of vision.[14,16,26] The patient reported here was also totally blind. Johnson, Harley and Horton[14] mention an unpublished case of R. W. Johnson in which vision was lost in one eye. Of these cases, at least ten showed evidence in the fundi of partial or complete occlusion of the central retinal artery. In some cases, the changes in the fundi were considered insufficient to account for the severe degree of visual loss, and it was suggested that the "occlusive episode had occurred in vessels too far back in the optic pathways" to produce the expected retinal lesions.[14] A similar situation existed in the present case and the same conclusions were drawn; however, there later developed the typical ophthalmoscopic picture of central retinal artery occlusion, approximately three weeks after total loss of vision.

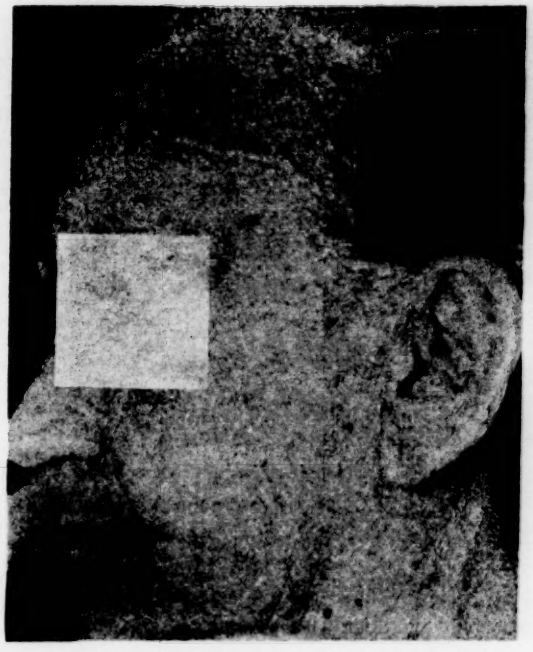

FIG. 1. *Profile photograph of the patient showing prominent thrombosed left temporal artery.*

Blindness is due to involvement of the nutrient arteries of the optic nerve and retina by the same inflammatory process which affects the temporal arteries. Johnson, Harley and Horton[14] have suggested a spread of the process from the anterior deep temporal artery through an anastomosis with the lacrimal branch of the ophthalmic artery to the central retinal artery, which sends an anterior and posterior branch to the optic nerve. However, since the disease definitely appears to be an arteritis which might involve any branches of the carotid artery and not merely a temporal arteritis as previously supposed, it would seem unnecessary to postulate such a spread.

That the location of the vascular lesion is usually the anterior portion of the visual pathways, probably at or anterior to the optic chiasm, is further suggested by the loss of pupillary light reflexes in the cases of blindness.[5,16,26]

An interesting finding in three cases [5,14,26] which was also noted in the present one, was that initially loss of vision occurred in the lower half of the field of vision. The exact significance of this is uncertain.

Diplopia was present in four patients,[7,26] and ptosis of the eyelids in two.[13,26] These findings presumably were due to involvement of the arterial supply of the oculomotor nerve.

Symptoms referable to involvement of the cerebrum, often with permanent mental changes, have been encountered in twelve cases. Bain's patient[6] was disoriented but recovered completely. One patient was left with mental sluggishness and lethargy.[9] Delirium, headache and dizziness led to consideration of a brain tumor in one case,[12] in which an abnormal colloidal gold curve and positive Pandy test on the spinal fluid were found; recovery was complete. Irritability and retardation of thought are reported by Kilbourne and Wolff in their case.[17] Bower's patient[8] re-entered the hospital nine months after the subsidence of her temporal arteritis, with weakness, vomiting, and then coma which lasted five days. This patient was hypertensive and arteriosclerotic, and a cerebrovascular accident could not be ruled out; however, the author considered a cerebral arteritis more likely. She recovered from this episode with no definite sequelae. Chasnoff and Vorzimer[24] believed that their patient's disorientation, coma and subsequent death were due to multiple cerebral thromboses. Cooke and co-workers[26] report a case with disorientation and mental deterioration in which old and recent multiple cerebral thromboses were found at autopsy. Another of their patients became deaf, disoriented, comatose and expired. Autopsy revealed multiple arterial thromboses in the brain. The case reported here showed neurological signs of bilateral cerebral involvement, irrationality and coma, followed in one week by death.

In approximately 25 per cent of the cases reported, the patients have complained of

FIG. 2. *Low power photomicrograph of biopsy specimen. Note the organized thrombus in the lumen. The intima is hypertrophied due to fibroblastic proliferation. The media, which lies between the disrupted internal elastic lamina (L) and the infiltrated adventitia (A) is almost completely replaced with a granulomatous lesion, consisting of multinucleated giant cells, epithelioid cells, leukocytes and necrotic muscle fibers. (Elastic tissue stain.)* × 60.

FIG. 3. *High power view of wall of artery, showing a zone of granulomatous tissue with many giant cells, outside of which are seen some remaining smooth muscle fibers. The adventitia is infiltrated with lymphocytes. (Hematoxylin-eosin stain.)* × 120.

aches and pains in the extremities and back. In some, this has consisted of a generalized muscle aching or joint pains sometimes associated with swelling,[5,10,25,26] while in others there has been clinical evidence of involvement of peripheral arteries, with pain and tenderness along the course of an artery, circulatory disturbances and thrombosis.[5,11,24,26] These symptoms usually have preceded the onset of headache and temporal arteritis.[23,26]

There have been no cases showing evidence of involvement of the smaller visceral arteries as is so often seen in periarteritis nodosa.

Laboratory Findings. A leukocytosis of variable degree has been constant, reaching as high as 17,000;[22] the average is about 12,000 per c. mm. A slight to moderate anemia has often been found, which may be attributed to the chronic infection although in some cases there were probable pre-existing causes. Eosinophilia has been conspicuously absent in all of the cases studied.

Renal and hepatic functions, when tested, have revealed nothing significant. Blood chemistry studies have been essentially normal. The cerebrospinal fluid has been examined in only a few cases; Schaefer and Sanders[12] found a positive Pandy test and an abnormal colloidal gold curve; Cooke and his associates[26] reported an elevation of spinal fluid protein in three cases, in one 130 mg. per cent, and in the other two 70 mg. per cent. In the present case, the spinal fluid was normal at first but showed a protein of 95 mg. per cent when cerebral involvement developed. The electrocardiograms have shown only the expected changes in the age group afflicted by this disease.

Spurred by the clinical picture suggesting an infectious process, many workers have sought a bacterial etiologic agent. This search has revealed nothing significant, although several organisms have been cultured from biopsy specimens. Horton, Magath and Brown[1] found an actinomyces in their first two cases but decided that this

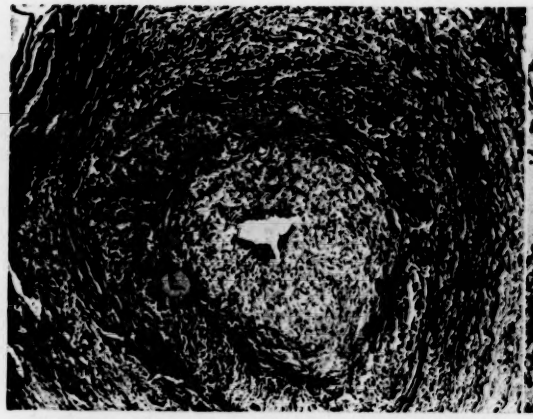

FIG. 4. *Low power view of artery showing the constricted lumen, hypertrophied intima, the disrupted internal elastic lamina (L) and the necrotic media. (Elastic tissue stain.)* × 60.

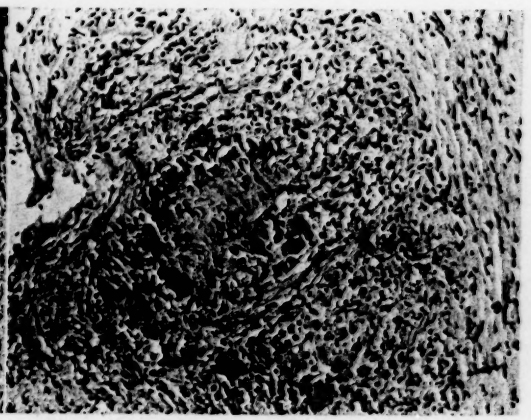

FIG. 5. *High power photomicrograph showing a tubercle-like focus in the media, with central necrosis surrounded by imperfectly formed giant cells and a broad zone of necrotic muscle fibers. (Hematoxylin-eosin stain.)* × 120.

was probably a contaminant. MacDonald and Moser[3] found Staphylococcus aureus and Bowers[8] cultured gram-positive cocci, probably staphylococci, from the biopsy. Dick and Freeman[7] obtained Streptococcus viridans from the biopsied artery. Blood cultures have been sterile; serum agglutination studies have been non-contributory. These variable findings indicate the need for continued careful search for a causative agent.

Pathology. From the case reports it is seen that a number of arteries besides the temporal have been involved. These include the retinal, occipital, facial, cerebral, carotid, radial, brachial, subclavian, aorta, celiac, mesenteric, femoral, coronary,[26] pulmonary, innominate, renal and iliac.[22] The possibility of widespread arterial involvement in this disease was not fully appreciated until the postmortem studies of Sproul,[22] Chasnoff and Vorzimer[24] and Cooke and his associates[26] revealed typical arteritis of the aorta and many of its branches. These patients during life had had symptoms suggesting inflammation of other arteries besides those of the head. Whether or not generalized involvement existed in those cases in which clinically the arteritis was limited to the head (75 per cent of the cases reported) is impossible to say.

There are several reports in the literature of chronic arteritis of the aorta and its branches, without the typical clinical picture of cranial arteritis. The pathological lesion as reported in most of these cases was essentially similar to that seen in the disease under discussion. Gilmour[20] reported four cases under the title of "giant cell chronic arteritis" which he considered the same as cranial arteritis. This conclusion seems justified in his Cases 2 and 3, but the other two cases do not fit the syndrome clinically or pathologically. Sproul and Hawthorne[18] described similar histologic changes in the aorta and iliac arteries in two cases, with involvement of the carotids in one of these. Barnard[21] reported a case with chronic granulomatous arteritis of the coronary and internal carotid arteries which he considered tuberculous but which Gilmour believed was the same as in his cases. While these cases vary in important respects from the typical syndrome, the similarities presented suggest a definite relationship the exact nature of which remains to be worked out.

Histopathologically, there has been a great deal of similarity in the type of lesion

found, all authors reporting a granulomatous panarteritis quite similar to that seen in periarteritis nodosa. In fact, some have reported that the lesion is microscopically indistinguishable from that of periarteritis.[5] The sections have shown pronounced thickening of the arterial wall due to a granulomatous process involving all three coats, with narrowing or complete occlusion of the lumen; thrombosis has been present in some cases. The intima has been found hypertrophied, due to fibroblastic proliferation, while the media usually has shown necrosis with formation of granulomatous tissue containing epithelioid cells and foreign body giant cells. The adventitia and media have been seen to be infiltrated with lymphocytes and some polymorphonuclear cells. Eosinophilic infiltration has been reported in four cases.[8,10,11,17] No aneurysmal dilatations, such as are seen in periarteritis nodosa, have been described. This, with the characteristic finding of giant cells, serves to differentiate the two conditions pathologically.

Course and Prognosis. This disease has been benign and self-limited in most instances, lasting from one to thirty months.[26] Relapses have occurred in several cases.[1,15] The arterial inflammation and constitutional disturbance have gradually subsided, but visual impairment has persisted in every patient so afflicted, and residual cerebral damage has been reported.[9,17]

It has become increasingly apparent as more case reports appear in the literature that this disease is not as benign as was formerly supposed. There have been three cases reported in which death followed a terminal picture of severe cerebral involvement.[24,26] At autopsy, all three showed active arteritis of many arteries of the body with multiple cerebral thromboses. The patient reported here died under very similar circumstances. Other patients have expired within two to twenty-four months of the onset of arteritis of causes considered to be unrelated.[3,22,26] While it is extremely difficult to ascertain accurately the cause of death in some of these elderly patients when postmortem studies have not been done, the time interval and circumstances suggest that death may have been due to arteritis in some cases. Thus, while the majority of these patients may expect eventual recovery after a rather prolonged and often disabling course, it must be recognized that this disease carries with it a definite mortality risk.

Treatment. There is no specific treatment for this disease. The usual supportive measures of diet, sedatives and analgesics are indicated. Biopsy of the temporal artery has often been followed by definite relief of the headache and pain,[1,4,8,16,19] but has had no effect on the course of the disease otherwise.[3,10,13,15,16] After all other treatment failed, Schaefer and Sanders[12] treated their patient on the Sanders oscillating bed, with results which they describe as remarkable. The rationale for this therapy was its use in peripheral vascular disease. Dantes[27] tried local irradiation of the temporal regions with no beneficial results.

Until the etiology and causative agent are definitely determined, the use of chemotherapy would be empirical. However, it would be of interest to try intensive sulfonamide, penicillin or streptomycin in an early case. Admittedly, such an experiment would be difficult to evaluate because of the rarity of the disease and variability of the course. Sulfonamides have been tried previously without definite benefit.[15] Anticoagulant therapy with heparin and dicumarol might be of value in preventing thrombosis, especially when blindness or cerebral damage threatens.

CASE REPORT

S. M., a seventy-one year old, white, single seamstress entered the Salt Lake General

Hospital on March 13, 1946, because of loss of vision in both eyes. The patient stated that she had been in good health until two months prior to admission, at which time she was suddenly struck with a whirling sensation, accompanied by pain in the back of her head. She immediately began to experience severe headache in the occipital region; this headache was dull and varied in intensity from time to time. Aspirin afforded some relief. Soon after, she noticed an aching pain involving the face and the neck; at this time, the skin of the face and scalp was quite tender to the touch; pain was pronounced on mastication. One week after the onset of headache, she noticed that the temporal arteries were becoming very prominent and tender, and there was redness of the overlying skin as well as intense throbbing pain. In association with the headaches and pain, the patient began feeling weak and ill, had a poor appetite and may have had some fever, although her temperature was never taken. She experienced drenching night sweats but had no chills. Over a period of several months, she lost approximately eighteen pounds. These symptoms persisted with some slight gradual improvement, until ten days before admission, when she began seeing flashes of colored light. Vision became blurred, then completely lost over a period of two days. The upper half of the visual field had been preserved somewhat longer than the lower half.

Admission examination revealed a thin, chronically ill woman, showing evidence of weight loss. Temperature was 100.0°F., pulse, 84, blood pressure 130/80. Both temporal arteries were very prominent, tortuous, somewhat nodular and cord-like; pulsations were not palpable. There was no redness of the overlying skin and only moderate tenderness. Vision was entirely absent in both eyes. The pupils were moderately dilated and fixed to light. There was no increase in ocular tension. The optic disks were swollen, with blurred margins and some elevation, especially on the left; both disks were definitely pale. A small hemorrhage was visible in the right eye in the inferior temporal quadrant. The blood vessels appeared normal. There were no exudates. The tongue was somewhat red with moderate atrophy of the papillae. The patient was edentulous. Careful search failed to reveal any evidence of sinusitis or other infection in the head. The peripheral arteries were not unduly firm, and the dorsalis pedis pulses were palpable. Neurological examination was normal. There were no significant findings in the chest or abdomen.

Laboratory studies revealed a normal urine on numerous occasions, a border-line normocytic anemia, corrected erythrocyte sedimentation of 44 in one hour (Wintrobe), and white count of 9,200 with a normal differential. Eosinophilia was not observed on repeated counts. Blood urea nitrogen was 12 mg. per cent, total protein 6.0 Gm. per cent with 4.7 Gm. albumin and 1.3 Gm. globulin; plasma fibrinogen was elevated to 756 mg. per cent, the normal range with the method used being 200 to 320 mg. per cent. Serology was negative as was the tuberculin test. Serum agglutinations for typhoid, paratyphoid, brucellosis, Rocky Mountain spotted fever, tularemia and cold hemagglutinins were negative. Blood cultures were sterile. Spinal fluid was entirely normal, as were renal function tests. One electrocardiogram was within normal limits.

Chest and sinus roentgenograms were essentially normal. Skull films revealed slight erosion of the dorsum sellae, which was considered not significant by the neurosurgical consultant.

A biopsy specimen taken from the right temporal artery was found to be thickened, cord-like and ischemic. Microscopically, a granulomatous panarteritis was seen. The lumen was almost occluded due to intimal hypertrophy produced by fibroblastic proliferation. In some sections an organized and recanalizing thrombus was visible. The entire wall, especially the media, was involved in a granulomatous process, with round cell infiltration, epithelioid cells and foreign body giant cells. There was some necrosis of the media, although this was not universal. The internal and external elastic laminae were disrupted and reduplicated. Ziehl-Neelsen stain failed to reveal any acid-fast bacilli. Cultures in broth and Sabouraud's media were sterile.

On the day of admission, the severe headaches ceased and the patient suffered only occasional aching of the back of the head and neck. No

more pain was experienced in the temporal areas. Her general condition improved progressively under symptomatic treatment, although low-grade fever persisted for three weeks, the highest being 101.8°F. The temporal arteries gradually decreased in prominence and pulsation became once more palpable.

Of major interest were the changes which occurred in the eyegrounds under observation. The swelling of the optic disks subsided gradually, while the pallor increased. Eleven days after admission, fragmentation and slowing of the blood stream appeared suddenly in the veins of the right retina. Over a period of twelve hours this had progressed to complete ischemia with pallor and cloudy swelling of the retina. The vessels were seen as fibrous strands; an occasional static clump of red cells could be seen in the veins. This picture remained essentially unchanged for three days, at which time blood was once more seen to flow, and the process was largely reversed, although some fragmentation of the stream, pallor of the retina and slight constriction of the arteries still remained. The day after the occlusion of the right central retinal artery occurred, a similar process began in the left eye, although complete occlusion was never reached. Circulation in this eye returned to approximately the preexisting status in four days. These eyeground changes occurred in the face of clinical improvement in every other respect.

Upon discharge from the hospital on April 6, 1946, the patient was afebrile, with a fair appetite but still quite weak. Vision was totally absent. Her condition remained essentially the same at home until April 21, 1946, when it was noted that she seemed to be getting weaker and was unable to help herself. On the day of admission, April 24, 1946, her family noticed that she did not move her left arm or leg, and was unable to close her left eye completely.

Admission examination this time revealed an emaciated, very weak woman, who was rather restless, moving her right arm and leg aimlessly. The entire left side was involved in a hemiparesis with a positive Babinski and ankle clonus. She talked irrationally and obeyed commands poorly. There was no fever; blood pressure was 128/72. The temporal arteries were less prominent than upon discharge and pulsation was definite. The pupils were dilated and fixed and the eyegrounds once more showed partial occlusion of the central retinal arteries. The remainder of the examination was essentially the same as on previous admission.

The white count was 6,000 per c. mm., with a normal differential count, the hematocrit was 36 cc. per cent and the corrected sedimentation rate was 32 mm. (Wintrobe). Urinalysis was normal. The spinal fluid was normal except for a protein content of 95 mg. per cent. Blood urea nitrogen was 14 mg. per cent.

The patient became increasingly weaker and lapsed into coma two days after admission. The signs of cerebral involvement became bilateral, and the central retinal artery occlusion became practically complete just prior to death. The temperature and pulse rose progressively, the coma deepened and she expired one week after admission. Permission for necropsy was denied.

COMMENT

The case presented here is entirely typical of the syndrome of "temporal arteritis," having many features in common with other cases previously reported. As has been frequently noted before, the constitutional symptoms of malaise, weakness, anorexia, fever and sweats, with headache, pain and tenderness involving areas of the head other than the temporal, preceded the appearance of the characteristic involvement of the temporal arteries. As in a number of other cases cerebral signs and symptoms developed which are best explained on the basis of involvement of the cerebral arteries. From the picture presented by this patient and most preceding ones, it is obvious that inflammation usually occurs in one or more of the other branches of the carotid artery, such as the retinal, occipital, cerebral, external maxillary, etc. For this reason, Kilbourne and Wolff have suggested that this disease be renamed "cranial arteritis." This term, while more fitting than "temporal arteritis," is not entirely satisfactory because such a term is localizing, rather

than etiologic, and fails to take into account the fact that a number, if not all, of these cases may have involvement of arteries other than the branches of the carotid artery. Still, inasmuch as the majority of patients have symptoms limited to the head, and until the etiology and extent of vascular involvement have been determined, "cranial arteritis" appears to be the best name yet suggested.

Although this disease is relatively benign, visual impairment is frequent and usually severe and cerebral involvement is moderately common and potentially fatal. Therefore, it is suggested that chemotherapy and anticoagulants be tried in early cases. The present case was first seen when the process seemed to be subsiding, otherwise such treatment would have been instituted. When the central retinal artery occlusion occurred, anticoagulant therapy was considered but decided against because optic atrophy was already present. This decision was fortunate, inasmuch as the subsequent reversal of eyeground changes would probably have been attributed falsely to the anticoagulants.

Careful search in this case failed to reveal any evidence of vascular involvement elsewhere in the body. The signs usually sought for in periarteritis nodosa were conspicuously absent here, as in most other cases studied. Pathologically, the presence of giant cells and the absence of aneurysmal sacs in the wall of the affected vessel served in this case, as well as in the previous cases, to differentiate this condition from periarteritis. When the complete clinical and pathological picture is known, diagnosis is not difficult and is sufficiently distinctive to merit consideration as a definite disease entity. The place it will eventually assume among the rest of the arterial diseases is not yet apparent, inasmuch as the lack of real knowledge in this group of diseases is profound.

SUMMARY AND CONCLUSIONS

1. Cranial arteritis is a rare, usually benign disease affecting the aged, predominantly females.

2. The symptom complex is well defined, consisting of signs and symptoms referable to inflammation and thrombosis of the temporal and other arteries of the head, as well as a systemic reaction of a type usually associated with infection.

3. Although in the majority of cases the arteritis appears to be limited to the head, clinical evidence of involvement of other arteries is moderately common. Postmortem examination of several such cases has revealed inflammation of the aorta and many of its branches.

4. Visual impairment is relatively frequent and is due to involvement of nutrient arteries of the optic nerve and retina.

5. The etiology is unknown but the constitutional reaction and the frequent finding of preceding or concomitant infection in the head make an infectious process appear most likely.

6. The typical histopathological lesion is that of a granulomatous panarteritis with foreign body giant cells.

7. Although the prognosis for life is relatively good, extensive arterial involvement, especially of the cerebrum, may prove fatal.

8. Treatment is non-specific. However, an adequate trial of chemotherapy and anticoagulants might be of value in early cases.

9. The clinical and pathological picture is sufficiently well defined to allow this condition to be designated as a distinct disease entity.

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Editorial

Present Status of Vitamin Requirements

THE latest revision of recommended dietary allowances by the Food and Nutrition Board, National Research Council,[1] includes an authoritative current estimate of vitamin requirements and provides a rational basis for prevention of deficiencies, still a confused and controversial subject. The allowances indicated include a factor of safety of at least 30 per cent to make provision for persons whose requirements may exceed the average need.[2]

The daily *vitamin A* intake should be 5,000 I. U. for the average man weighing 70 kg. and the average woman weighing 56 kg., with increases to 6,000 I. U. in the latter half of pregnancy and to 8,000 I. U. in lactation. Children under one year should receive 1,500 I. U. daily, then 2,000 I. U. from one to three years and a further daily increase of 500 I. U. every three years until the adult level of 5,000 I. U. is reached at puberty. These allowances are based on the premise that carotene contributes two-thirds of the vitamin A value in the average diet and that carotene has half or less the value of vitamin A.

The *thiamine* requirement is estimated at 1.2 mg. to 2.0 mg. daily for men and 1.1 mg. to 1.5 mg. daily for women, depending on activity. In the latter half of pregnancy 1.8 mg. is recommended, with 2.0 mg. daily during lactation. Children under one year should receive 0.4 mg. daily. Daily increments of 0.2 mg. every three-year period thereafter are suggested until the thirteenth year. Between the ages of thirteen and fifteen, girls should receive 1.3 mg. daily, boys 1.5 mg.; between the ages of sixteen and twenty, girls require 1.2 mg. daily, boys 1.8 mg.

The daily recommended allowance of *riboflavin* is 1.6 mg. to 2.6 mg. for men and 1.5 mg. to 2.0 mg. for women, depending on activity. The requirement is increased to 2.5 mg. in the latter half of pregnancy and to 3.0 mg. daily in lactation. Infants should receive 0.6 mg. daily, children one to three years 0.9 mg. daily. Further daily increases of 0.3 mg. are indicated every three years until adult levels are reached at puberty.

Twelve to 20 mg. of *niacin* (nicotinic acid) should be provided daily for men and 11 mg. to 15 mg. for women, with increases to 18 mg. daily in late pregnancy, 20 mg. during lactation. Infants require 4 mg. daily, young children need 6 mg. to 8 mg. daily, with increases up to adult requirements at the age of thirteen.

As regards factors of the B complex other than thiamine, riboflavin and niacin, the report states that the requirements of these cannot be given at the present time. They are believed to be sufficiently supplied, however, by foods adequate in the B vitamins for which requirements are known.

The daily need for *ascorbic acid* is 75 mg. for men and 70 mg. for women, rising to 100 mg. in late pregnancy and 150 mg. in lactation. Infants require 30 mg. daily; children one to three years, 35 mg.; four to six years, 50 mg.; seven to nine years, 60 mg.; ten to twelve years, 75 mg.; thirteen to twenty years, 80 mg. daily for girls and 90 to 100 mg. for boys.

Normal adults probably have little need for *vitamin D*, although ingestion of small amounts may be desirable for persons hav-

[1] Reprint and Circular Series #122, National Research Council, 1946.

[2] WILDER, R. M. Misinterpretation and misuse of the recommended dietary allowances. *Science*, 101: 285, 1945.

ing no opportunity for exposure to clear sunshine and for elderly persons. In late pregnancy and lactation the requirements are estimated to be 400 I. U. to 800 I. U. daily. Infants under one year require 400 I. U. to 800 I. U. daily, growing children need 400 I. U. daily.

The report states that these allowances "can be met by a good diet with a variety of natural foods." Such a diet, according to Jolliffe,[3] should include at least four eggs weekly; one serving daily of citrus fruit or tomato or their juices, or fresh uncooked salad greens; one quart of milk daily for children, with an extra source of vitamin D (for adults, one pint of milk daily or its equivalent in cheese); one serving daily of lean meat, fish, poultry or seafood; one serving daily of a cooked leafy green or yellow vegetable; one serving daily of another vegetable or fruit; one portion daily of enriched or whole grain bread or cereal.

[3] JOLLIFFE, N. The preventive and therapeutic use of vitamins. *J. A. M. A.*, 129: 613, 1945.

Book Reviews

"A MANUAL of Tropical Medicine"* is the result of a collaborative effort by authorities on tropical medicine of the Army Medical School, together with civilian consultants, and was prepared under the auspices of the Division of Medical Sciences of the National Research Council. Although designed primarily as a practical reference manual for medical officers in the field, the book provides a concise and eminently satisfactory text for medical students and offers a convenient summary of up-to-date information for physicians and other persons concerned with public health.

The manual is divided into eleven sections dealing successively with the viruses, rickettsial diseases, spirochetal diseases, bacterial diseases, mycotic diseases, protozoal diseases, helminthic diseases, nutritional diseases, miscellaneous conditions, medically important arthropods and laboratory diagnostic aids. Each clinical topic is discussed in an orderly manner under all or part of the following heads: synonyms, definition, distribution, etiology, epidemiology, pathology, clinical characteristics, diagnosis, treatment and prophylaxis.

The text is concise but is more detailed and complete than is usually found in manuals or compendiums. A noteworthy omission is the failure to mention penicillin in the treatment of any of the spirochetal diseases. The illustrations are profuse and finely reproduced from photographs, photomicrographs, charts and drawings. The pictorial diagrams which outline the epidemiology of diseases by graphically portraying the life-cycles of the etiological agents are especially well done. In the section on malaria there are six colored plates which reproduce, with considerable fidelity, the various stages of plasmodial development within the erythrocyte.

The final section on laboratory diagnostic aids is to be commended for the apt selection and clear presentation of methods which are suitable for use in the field or modestly equipped laboratory.

The book is well printed on a good grade of glazed paper and is attractivvly bound in a limp fabrikoid cover. A short bibliography of standard references is presented, but in order to conserve space and paper the authors make no bibliographic references in the text. The index, which is often omitted from works of this type, is comprehensive and facilitates ready reference to any part of the text.

The authors and their numerous colleagues are to be congratulated for the production of a timely, authoritative work which is a worthy and useful companion of standard textbooks on tropical medicine.

H. M. R.

* A MANUAL OF TROPICAL MEDICINE. Prepared under the auspices of the Division of Medical Sciences of the National Research Council. By Colonel Thomas T. Mackie, M. C., A. U. S., Executive Officer, Tropical and Military Medicine, Army Medical School, Major George W. Hunter, III, Sn. C., A. U. S., and Captain C. Brooke Worth, M. C., A. V. S. Philadelphia and London, 1945. W. B. Saunders Company. Price $6.00.

"Diseases of the Adrenals"* arrives on the scene as an opportune and welcome addition to a modern medical library. Dr. Soffer has compiled a thorough review of a difficult subject in readable, well organized form, handsomely bound and printed, and to be commended for its large and complete review of the literature. Beginning with brief reviews of the antaomy and embryology of the adrenals, the author continues with a chapter on chemical and mechanical technics before going on with a discussion of physiology of the adrenal glands, its various disorders and their modern management.

In recent years a vast amount of clinical and experimental work has been carried out on the adrenal glands. Although such illnesses as Addison's disease and Cushing's syndrome are but rarely encountered by the general practitioner, the physiological disturbances that take place have an important bearing on our understanding of normal fluid, electrolyte and metabolic functions. There are also possible implications in such apparently unrelated fields as shock, hypertension and antibody formation.

* Diseases of the Adrenals. By Louis J. Soffer, M.D. Pp. 304, with 44 illustrations. Philadelphia, 1946. Lea & Febiger. *Price* $5.50.

This volume can be criticized for its tendency to be somewhat over-thorough and repetitive in places. For example, discussions of the mechanism of pigmentation, of renal function changes and hypoglycemia are given in chapters on physiology and then repeated with almost exact wording and with the same references to the literature under the heading of the clinical picture of Addison's disease. Simplicity of sentence structure and brevity are often lacking. Some confusing irrelevancies appear, particularly in those paragraphs devoted to endocrine gland interrelationships. Two illustrations appearing several pages apart, demonstrating osteoporosis of the vertebrae, are practically identical if not the same. A few minor points are occasionally noted on which debate is possible. For example, it is stated that impotence is often present in the male with Addison's disease. The reviewer has, on the other hand, been impressed by the lack of change in sexual function in patients with this disorder.

In spite of the occasional tendency to duplicate literature, reviews and physiological discussions under several headings, this text can be recommended to both students and specialists on the subject as a work of reference. G. A. P.

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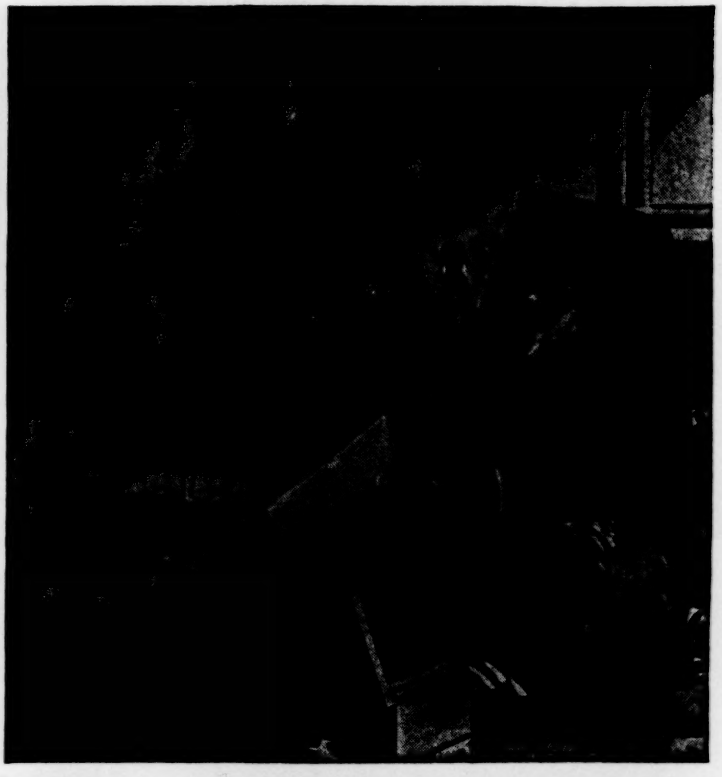

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1. J.A.M.A. *129*:1080, Dec. 15, 1945
2. Illinois M. J. *88*:85, August, 1945

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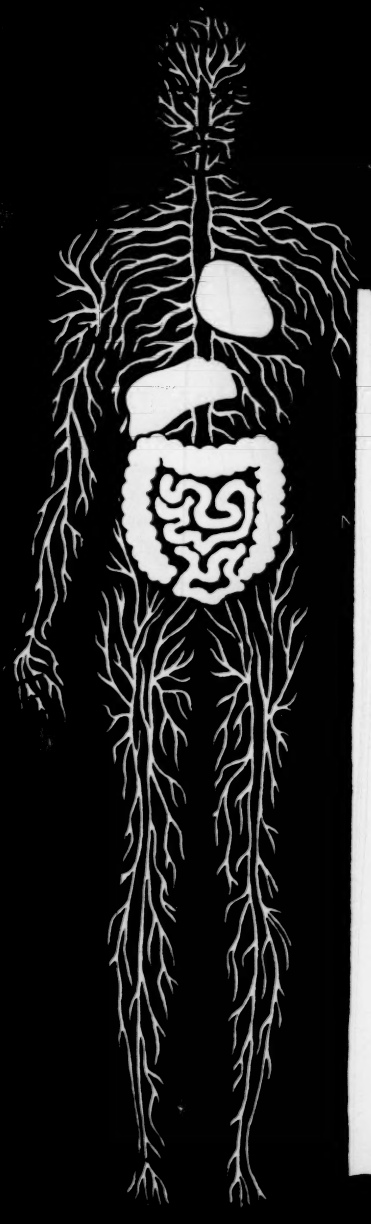

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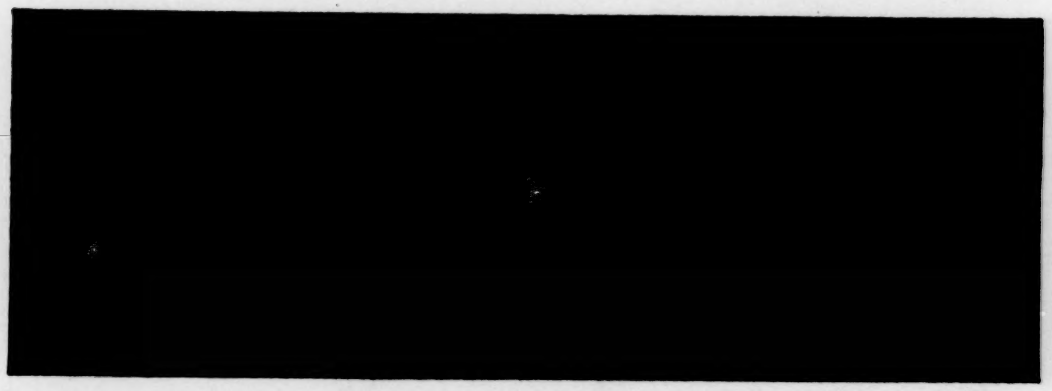

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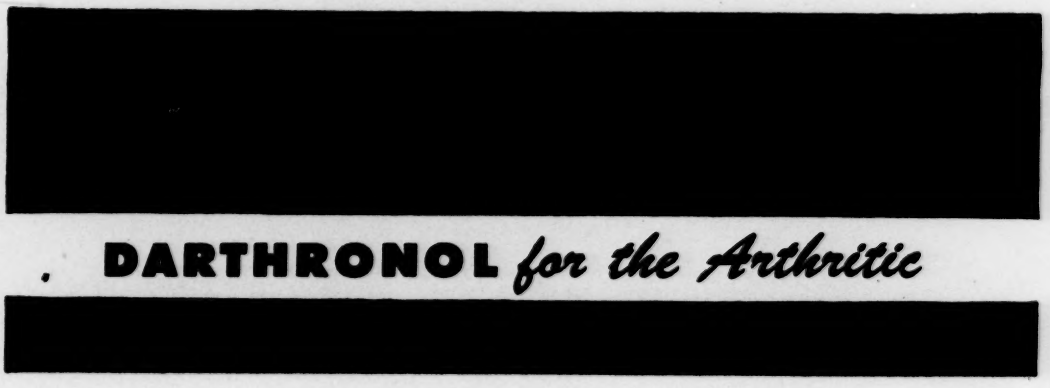

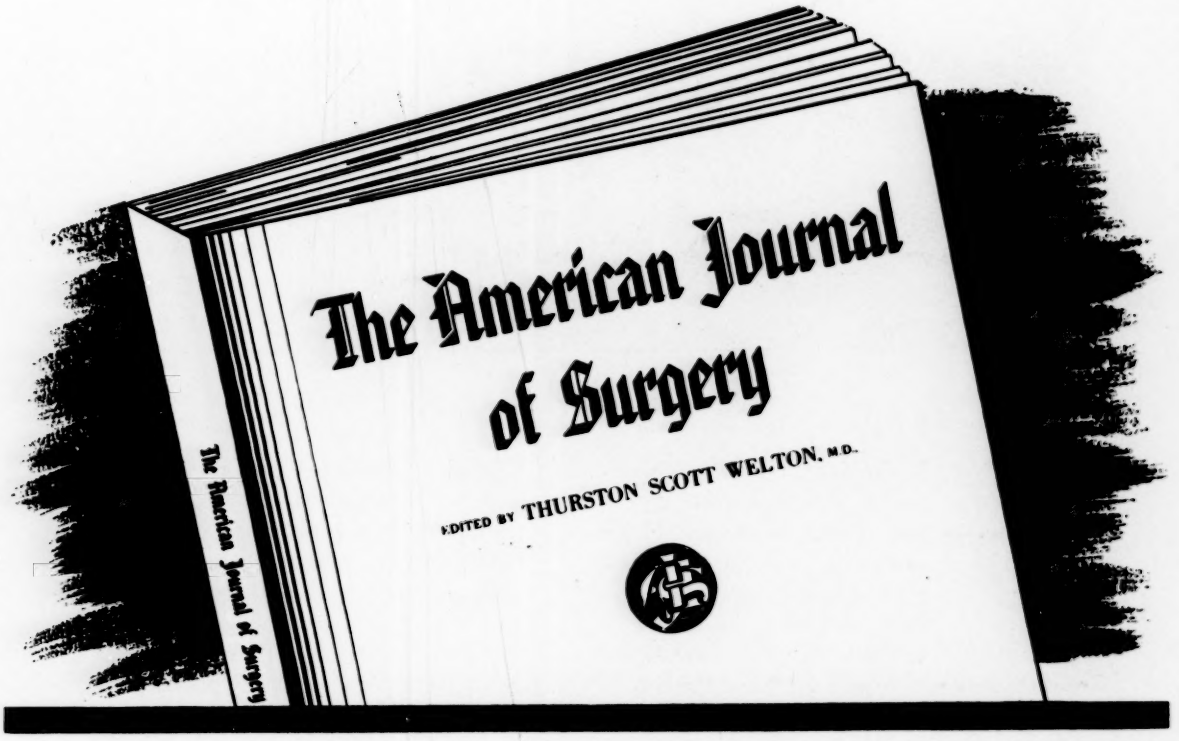

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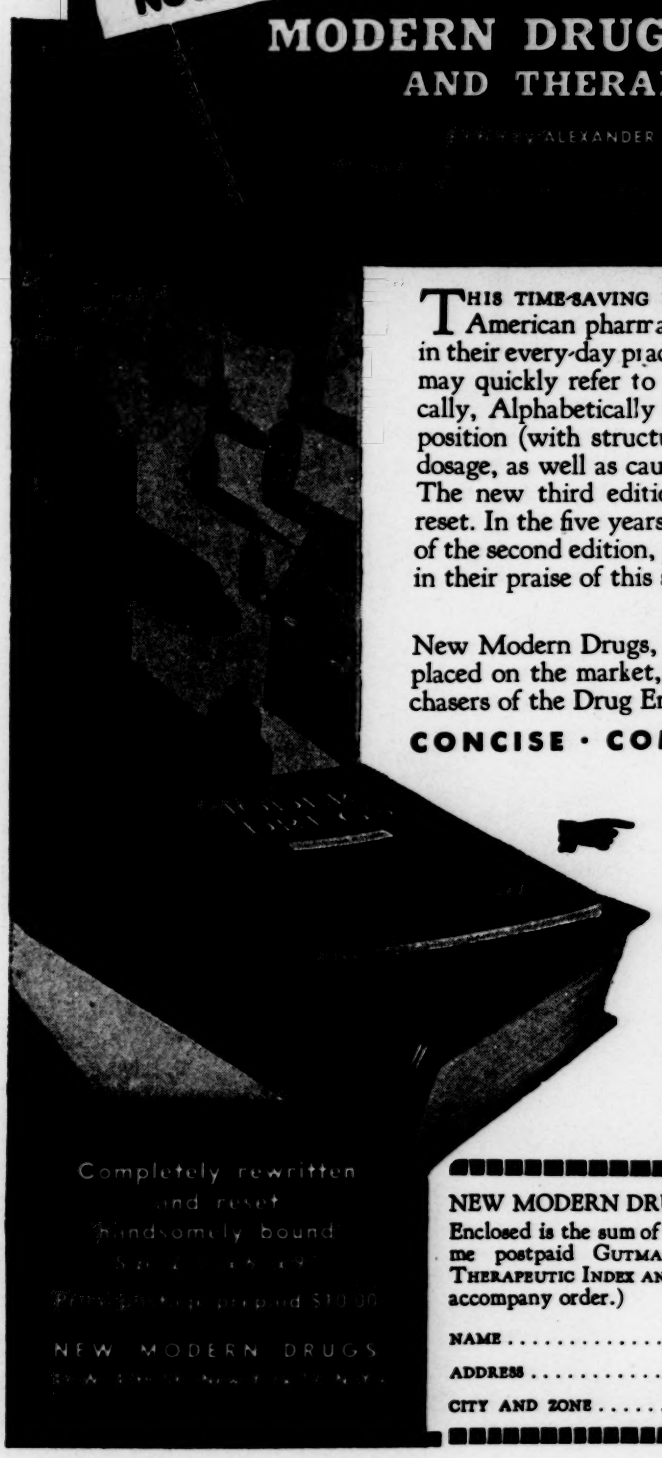

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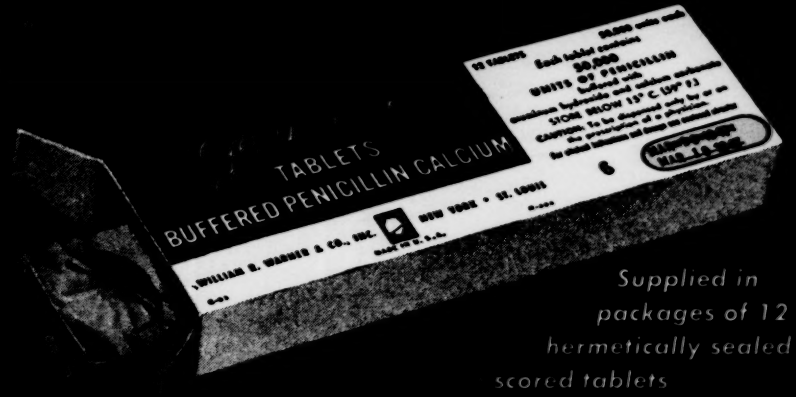

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